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OCCUPATIONAL EXPOSURE TO

XYLENE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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1975

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

HEW Publication No. (NIOSH) 75–168

PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on xylene by members of my staff, the valuable and constructive comments presented by the Review Consultants on Xylene, by the ad hoc committees of the American Industrial Hygiene Association and the American Medical Association, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by William A. Burgess on respiratory protection. The

NIOSH recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on xylene. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.

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The Office of Research and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for xylene. Tabershaw-Cooper Associates developed the basic information for consideration by NIOSH staff and consultants under contract No HSM-99-73-39. Bryan D. Hardin had NIOSH program responsibility and served as criteria manager.

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR XYLENE

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I. RECOMMENDATIONS FOR A XYLENE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to xylene in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of workers over a working lifetime; compliance with all sections of the standard should therefore prevent adverse effects of xylene on the health and safety of workers. The standard is measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. The criteria and standard will be subject to review and revision as necessary.

Regardless of the source of raw materials from which produced, "xylene" (also known as "xylol" or "dimethylbenzene") refers to any one of or combination of the isomers of xylene: ortho-, meta-, or para-dimethylbenzene. The term "xylene" will be used throughout this document. "Exposure to xylene" is defined as exposure above half the recommended time-weighted average environmental limit. If "exposure" to other chemicals also occurs, for example from contamination of xylene with benzene, provisions of any applicable standard for the other chemicals shall also be followed.

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure to xylene shall be controlled so that workers are not exposed to xylene at a concentration greater than 100 parts per million parts of air by volume (approximately 434 milligrams per cubic meter of air) determined as a time-weighted average (TWA) exposure for up to a 10-hour workday, 40-hour workweek, with a ceiling concentration of 200 parts per million parts of air by volume (approximately 868 milligrams per cubic meter of air) as determined by a sampling period of 10 minutes.

(b) Sampling, Collection, and Analysis

Procedures for collection and analysis of environmental samples shall be as provided in Appendices I and II or by any method shown to be equivalent in accuracy, precision, and sensitivity to the method specified.

Section 2 - Medical

Comprehensive preplacement and biennial (every 2 years) medical examinations should be provided for all workers subject to "exposure to xylene." The history and examination should be directed toward, but not limited to, the incidence of headaches, nausea or other gastrointestinal disturbance, dizziness, and of alcohol consumption. Particular attention should be focused on complaints and evidence of eye, mucous membrane, or skin irritation. Laboratory tests recommended at the time of the biennial examination include a complete blood count, a routine urinalysis, and appropriate liver function tests.

Section 3 - Labeling (Posting)

(a) Labeling

Containers of xylene shall carry a label stating:

XYLENE
(XYLOL, DIMETHYLBENZENE)

WARNING! FLAMMABLE
HARMFUL IF INHALED OR SWALLOWED
IRRITATING TO SKIN OR EYES

Keep away from heat, sparks, and open flame.
In case of fire, use foam, dry chemical, or CO2.
Avoid breathing vapor.
Avoid contact with eyes, skin, and clothing.
Keep container closed.
Use with adequate ventilation.
Do not use for washing hands, floors, or equipment.

First Aid: In case of eye or skin contact with liquid xylene, wash with plenty of water. If eye contact, call a physician. If swallowed, call a physician. Do not attempt to induce vomiting.

(b) Posting

Areas where there is occupational exposure to xylene shall be posted with a sign reading:

XYLENE

WARNING! FLAMMABLE
HARMFUL IF INHALED OR SWALLOWED
IRRITATING TO SKIN OR EYES

Keep out heat, sparks, or open flames.
No smoking permitted.
In case of fire, use fire extinguishers. (Give location)
Avoid breathing vapor.
Avoid contact with skin, eyes, and clothing.
Provide adequate ventilation.

This warning sign shall be printed both in English and in the predominant language of non-English-speaking workers, unless they are other-

wise trained and informed of the hazardous areas. All illiterate workers shall receive such training.

Section 4 - Personal Protective Equipment

(a) Protective Clothing

(1) Chemical safety goggles, face shields, or safety glasses with side shields shall be provided by the employer and shall be worn in any operation in which xylene may splash into the eyes.

(2) Appropriate protective clothing, including gloves, aprons, suits, boots, or face shields, shall be worn where needed to prevent repeated or prolonged skin contact.

(b) Respiratory Protection

(1) Engineering controls shall be used wherever feasible to maintain xylene concentrations below the prescribed limits. Such control equipment shall be sparkproof. Compliance with the permissible exposure limit may not be achieved by the use of respirators except:

(A) During the time period necessary to install or test the required engineering controls.

(B) For nonroutine operations such as a brief exposure to concentrations in excess of the permissible exposure limit as a result of maintenance or repair activities.

(C) During emergencies when air concentrations of xylene may exceed the permissible limit.

(2) When a respirator is permitted by paragraph (b)(1) of this Section, it shall be selected and used pursuant to the following requirements:

(A) For the purpose of determining the type of respirator to be used, the employer shall measure, when possible, the atmospheric concentration of xylene in the workplace initially and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the xylene concentrations; this requirement shall not apply when only atmosphere-supplying positive pressure respirators will be used. The employer shall ensure that no worker is being exposed to xylene in excess of the standard because of improper respirator selection, fit, use, or maintenance.

(B) A respiratory protection program meeting the requirements of 29 CFR 1910.134 as amended shall be established and enforced by the employer.

(C) The employer shall provide respirators in accordance with Table I-1 below and shall ensure that the employee uses the respirator provided.

(D) Respiratory protective devices described in Table I-1 shall be those approved under the provisions of 30 CFR 11 as amended.

(E) Respirators specified for use in higher concentrations of xylene may be used in atmospheres of lower concentrations.

(F) The employer shall ensure that respirators are adequately cleaned, and that employees are instructed on the use of respirators assigned to them, and on how to test for leakage.

(G) Where an emergency may develop which could result in employee injury from overexposure to xylene, the employer shall provide respiratory protection as listed in Table I-1.

TABLE I-1

RESPIRATOR SELECTION GUIDE FOR PROTECTION AGAINST XYLENE

Multiples of TWA Limit	Respirator Type
Less than 10x	Chemical cartridge respirator with full facepiece and organic vapor cartridge(s).
Less than 50x	Gas mask (full facepiece) with a chin-style organic vapor canister.
Less than 100x	(1) Gas mask (full facepiece) with front or back mounted organic vapor canister. (2) Type C supplied air respirator with a full facepiece operated in the demand (negative pressure) mode. (3) Type C supplied air respirator with a full facepiece operated in the pressure-demand (positive pressure) or continuous flow mode. (4) Self-contained breathing apparatus with a full facepiece operated in the demand (negative pressure) mode. (5) Combination Type C supplied air respirator with full facepiece operated in the demand (negative pressure) or continuous flow mode and an auxiliary self-contained air supply operated in the demand (negative pressure) mode.
100x or more CAUTION! The lower explosive limit is approximately 11,000 ppm	(1) Self-contained breathing apparatus with a full facepiece operated in the pressure-demand (positive pressure) mode. (2) Combination Type C supplied air respirator with full facepiece operated in the pressure-demand (positive pressure) or continuous flow mode and an auxiliary self-contained air supply operated in the pressure-demand (positive pressure) mode.
Unknown concentration	Self-contained breathing apparatus with a full facepiece operated in the pressure-demand (positive pressure) mode.
Escape	(1) Gas mask (full facepiece) with chin style or front or back mounted organic vapor canister. (2) Self-contained breathing apparatus with full facepiece operating either in the demand (negative pressure) or pressure demand (positive pressure) mode.

Section 5 - Informing Employees of Hazards from Xylene

(a) Each employee exposed to xylene shall be informed at the beginning of his employment or assignment to a xylene area of the hazards, relevant symptoms, appropriate emergency procedures, and proper conditions and precautions for safe use or exposure. Each employee shall be instructed as to the availability of such information which shall be kept on file. Information kept on file shall include that prescribed in (b) below and shall be accessible to the worker at each place of employment where xylene is involved in unit processes and operations.

(b) Information as specified in Appendix III shall be recorded on US Department of Labor Form OSHA-20, "Material Safety Data Sheet," or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Emergency Procedures

For all work areas in which there is a reasonable potential for emergencies, procedures as specified below, as well as any other procedures appropriate for a specific operation or process, shall be formulated in advance and employees shall be instructed in their implementation.

(1) Procedures shall include prearranged plans for obtaining emergency medical care and for necessary transportation of injured workers.

(2) Firefighting procedures shall be established and implemented. These shall include procedures for emergencies involving release of xylene vapor. In case of fire, xylene sources shall be shut off

or removed. Containers shall be removed or cooled with water spray. Chemical foam, carbon dioxide, or dry chemicals should be used for fighting xylene fires, and proper respiratory protection and protective clothing shall be worn.

(3) Approved eye, skin, and respiratory protection as specified in Section 4 shall be used by personnel essential to emergency operations.

(4) Nonessential employees shall be evacuated from exposure areas during emergencies. Perimeters of areas of hazardous exposures shall be delineated, posted, and secured.

(5) Personnel properly trained in the procedures and adequately protected against the attendant hazards shall shut off sources of xylene, clean up spills, and immediately repair leaks.

(b) Engineering controls such as process enclosure or local exhaust ventilation shall be used to maintain xylene concentrations within the recommended environmental limits. All such control equipment shall be sparkproof. Ventilation systems shall be designed to prevent the accumulation or recirculation of xylene in the workplace and to effectively remove xylene from the breathing zones of exposed workmen. Exhaust ventilation systems discharging to outside air must conform with applicable local, state, and federal air pollution regulations. Ventilation systems shall be subject to regular preventive maintenance and cleaning to ensure maximum effectiveness, which shall be verified by periodic airflow measurements.

(c) Containers of xylene shall be kept tightly closed at all times when not in use. Containers shall be stored in accordance with the

provisions of 29 CFR 1910, and shall be protected from heat, corrosion, mechanical damage, and sources of ignition.

(d) Washing of hands, equipment, or structures with xylene shall be prohibited.

(e) Any spills of xylene shall be promptly cleaned up.

(f) Prior to maintenance work, sources of xylene and xylene vapor shall be eliminated to the extent feasible. If concentrations below the workplace air limit cannot be assured, respiratory protective equipment shall be used during such maintenance work.

(g) All metal dispensing containers shall be properly grounded.

Section 7 - Sanitation

(a) Food Facilities

Food preparation, dispensing (including vending machines), and eating should be prohibited in xylene work areas.

(b) Smoking

Smoking shall not be permitted in areas where xylene is used, transferred, stored, or manufactured.

Section 8 - Monitoring and Recordkeeping

Workroom areas shall not be considered to have xylene exposure if environmental levels, as determined on the basis of a professional industrial hygiene survey or by the judgment of the compliance officer, do not exceed half of the recommended time-weighted average limit. Records of these surveys, including the basis for concluding that air levels are at or

below half of the time-weighted average limit, shall be maintained until a new survey is conducted. Surveys shall be repeated when any process change indicates a need for reevaluation or at the judgment of the compliance officer. Requirements set forth below apply to areas in which there is xylene exposure.

Employers shall maintain records of environmental exposures to xylene based upon the following sampling and recording schedules:

(a) In all monitoring, samples representative of the exposure in the breathing zone of employees shall be collected. An adequate number of samples shall be collected to permit construction of a time-weighted average (TWA) exposure for every operation or process. The minimum number of representative TWA determinations for an operation or process shall be based on the number of workers exposed as provided in Table I-2.

TABLE I-2

SAMPLING SCHEDULE

Number of Employees Exposed	Number of TWA Determinations
1-20	50% of the total number of workers
21-100	10 plus 25% of the excess over 20 workers
over 100	30 plus 5% of the excess over 100 workers

(b) The first environmental samples shall be completed within 6 months of the promulgation of a standard incorporating these recommendations.

(c) Environmental samples shall be taken within 30 days after installation of a new process or process change.

(d) Samples shall be collected at least quarterly in accordance with Appendix I for the evaluation of the work environment with respect to the recommended standard.

(e) Environmental monitoring of an operation or process shall be repeated at 30-day intervals when the xylene concentration has been found to exceed the recommended environmental standard. In such cases, suitable controls shall be initiated and monitoring shall continue at 30-day intervals until two consecutive surveys indicate the adequacy of these controls.

(f) Sampling records shall be maintained so that exposure information is available for individual employees and shall indicate the type of personal protective devices, if any, in use at the time of sampling. Each employee shall be able to obtain information on his own environmental exposure.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to xylene. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents. It should be pointed out that any recommended criteria for a standard should enable management and labor to develop better engineering controls resulting in more healthful work practices and should not be used as a final goal.

These criteria for a standard for xylene are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, use of, or other occupational exposure to xylene as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large, and any extrapolation beyond occupational exposures is not warranted. It is intended to (1) protect against development of systemic effects, and

against local effects on the skin and eyes, (2) be measurable by techniques that are valid, reproducible, and available to industry and governmental agencies, and (3) be attainable with existing technology.

For many years, myelotoxicity (toxicity to the blood and blood-forming organs) has been attributed to xylene, primarily because of the close structural similarity which exists between xylene and benzene and the established effects of benzene on the blood and blood-forming organs. Xylene has been contaminated frequently with benzene. Current scientific evidence obtained from human and animal studies indicates that alkylation of the benzene ring, such as exists with xylene (dimethylbenzene), results in a loss of these blood effects. Benzene appears to be unique among the monocyclic aromatic hydrocarbons in these myelotoxic properties. Therefore, the major problem of xylene toxicity concerns its narcotic effects on workers, causing symptoms and signs such as muscular weakness, incoordination, and mental confusion which may pose a risk to both the worker and others.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Xylene, $C_6H_4(CH_3)_2$, (formula weight 106.16), also called dimethylbenzene or xylol, exists in 3 isomeric forms: 1,2 (ortho); 1,3 (meta); and 1,4 (para). The more important physical properties of these isomers are presented in Table X-1. [1]

Commercial xylene is produced both from petroleum and from coal tar. A typical petroleum product contains approximately 20% o-xylene, 44% m-xylene, 20% p-xylene, and 15% ethylbenzene. Xylene from coal tar generally consists of 10-15% ortho-, 45-70% meta-, about 23% para-, and 6-10% ethylbenzene. Commercial xylenes may also contain small amounts of toluene, trimethylbenzene, phenol, thiophene, pyridine, and nonaromatic hydrocarbons. [2,3] The possibility that commercial xylene may also contain benzene should not be ignored.

Total US xylene production in 1971 was 612,325,000 gallons, an increase of 13.9% over 1970. [4] Of this total, 609,419,000 gallons were from petroleum. Production from coke ovens has decreased rapidly in recent years (35.4% from 1970-1971) and totaled only 2,906,000 gallons in 1971. The US Tariff Commission report [4] did not include data reported by tar distillers because publication would have disclosed operations of individual companies.

Xylene can be easily chlorinated, sulfonated, or nitrated. [5] It is used as a solvent for some gums and resins, castor and linseed oils, rubber, and dibenzyl cellulose. [6] It is a constituent of paint, lacquers and varnishes, [5,6] inks, dyes, adhesives and cements, and cleaning fluids

[7]; it is also an additive in gasoline. [5-7] In the chemical industry it is used as a starting material for xylidines [5] and in the production of phthalic and terephthalic acids. [2,6] Other uses are in the manufacture of quartz crystal oscillators, hydrogen peroxide, perfumes, and insect repellents, [8] in the leather industry, in coating and impregnation of fabric and paper, and as a carrier in the production of epoxy resins. [2]

NIOSH estimates that approximately 140,000 workers are potentially exposed to xylene in the United States.

Historical Reports

Many early reports of xylene exposures involved exposure not to pure xylene but to mixed aromatic hydrocarbons. For example, in 1929 Stocke [9] reported that, although the term "xylene" was used in the occupational medical literature of the time, he found that the solvent called "xylene" in the intaglio printing industry might be pure xylene, pure toluene, a mixture of these, or a mixture containing benzene and paraffin hydrocarbons. Stocke examined approximately 40 workers exposed to these mixed solvents and observed symptoms of overexposure: headaches, nausea, feelings of drunkenness, and reduced alcohol tolerance. In 10 of these, selected because they were the most severely affected, there was no anemia, but Stocke did report a relative lymphocytosis. To explain the reduced alcohol tolerance, he hypothesized that alcohol facilitated the diffusion of xylene (and toluene) in the body, and in particular expedited their entry into the lipids of the central nervous system.

In 1931 Nelken [10] examined 399 intaglio printers and 276 other printers not exposed to xylene. Relative lymphocytosis was observed in 29%

of the intaglio printers and in 23.7% of the nonintaglio printers. An apparently significant difference in the incidence of leukopenia was observed, with 18.55% of the intaglio printers having a leukocyte count below 5,800, 15.03% below 5,500, and 9.29% below 5,000 compared to 13.64%, 8.18%, and 3.63%, respectively, among the nonintaglio printers. Nelken considered this evidence of poisoning caused by "xylene (or toluene and benzene)."

In the same year Rosenthal-Deussen [11] described the experience of 20 workers who were exposed to unknown concentrations of vapor of a commercial solvent, consisting of 35% benzene and its homologs, principally xylene. The major constituent(s) was not identified. Workers were exposed for 1-6 days while painting the inside of a tank that was not ventilated properly. Of the 20 workers exposed, 15 were reported as manifesting urinary abnormalities, among other signs and symptoms. There were 2 cases of anuria, 1 of which was fatal. In 13 cases the urine was described as "coffee-brown" in color. These included the 2 cases of anuria. In 2 other cases the urine was described as being red. With the limited environmental data available, it is impossible to say what role, if any, xylene may have played in the etiology of these disorders.

Hirsch [12] in 1932 investigated conditions in a print shop after 2 of its workers died of valvular heart disease. Suspecting benzene poisoning because 1 of the deceased workers was anemic and the other had aplastic anemia, Hirsch examined 34 workers. Despite the fact that some thinners contained up to 29% benzene and toluene, Hirsch concluded that xylene was responsible for the anemia observed because xylene predominated (up to 87%) in the solvents and thinners used. Overall, he observed a

moderate degree of anemia and relative lymphocytosis, but the latter was thought not to be necessarily occupationally related. Increases in urinary urobilin and urobilinogen were seen in 18 of 34 workers, with a very marked increase in 3 of them. Such an increase (ie, in the last 3 cases) may be regarded as an indication of liver damage. A majority of the workers were hypotensive. Radiography revealed pathological alterations of cardiac outline and size in 50% of the subjects, with dilatation of the aorta present in the majority of the abnormals. Hirsch attributed these phenomena to the "vasodilatory effect of xylene." Nineteen of the 34 subjects were also anemic with hemoglobin levels of below 95% Autenreith in 5 subjects, and a red cell count below 5 million/cu mm in 15 subjects. The observed hypotension might have been partly secondary to this anemia. Two years later in 1934, Verhoogen [13] also reported a fatal case of aplastic anemia and extreme leukopenia in a printer. Although he gave no details as to exposure, Verhoogen stated that the anemia was due to xylene exposure in a print shop. De Oliveira [14] in 1936 described a similar fatality due to aplastic anemia, but like Veerhoogen, [13] he failed to give any details concerning exposure except to state that the individual was exposed to xylene in the printing industry.

In 1935 Glibert [15] published 6 case reports involving pseudopernicious anemia and aplastic anemia which he ascribed to xylene exposure in the printing industry. The very imprecise meaning of the term "xylene" at that time was demonstrated by Glibert when he stated that the "commercial xylenes" used in the printing industry showed a variable composition, with "yellow or light xylene" being pure benzene with no trace of xylene, "green or dark xylene" being pure xylene, and some other xylenes actually being

toluene with 15% benzene. Obviously, the term xylene was applied to a variety of solvents, and even what was considered to be pure xylene must have been contaminated if it was green or dark in color, since pure xylene is colorless.

A detailed study of occupational disease associated with exposure to solvents in the printing industry was conducted in this country by Greenburg et al [16] in 1939. In this report toxicity was attributed to benzene, but the report provides an insight into the mixed nature of solvents in use at that time. In this study, benzene in the ink solvents and thinners ranged from 10-80% and other volatile solvents present included toluene, xylene, methylethyl ketone, petroleum naphtha, ethyl, butyl, and amyl acetate, and butyl and amyl alcohol. Thus, one must question the accuracy of those papers which reported "xylene" exposure in the printing industry through the 1940's. In most cases the thinners used probably consisted of a mixture of volatile solvents. Xylene probably was one of these, but benzene was almost certainly present as well.

Effects on Humans

In 1943 Nelson et al [17] investigated sensory response to 16 industrial solvent vapors by exposing "an average number of ten persons, of mixed sexes," to metered concentrations of solvent vapors for a period of 3-5 minutes. Based on the subjective responses of test subjects, xylene at 200 ppm was reported to cause irritation of the eyes, nose, and throat in a majority of those exposed. A majority also estimated that 100 ppm would be a satisfactory 8-hour exposure level. The authors did not report the lowest concentration which was irritating to any subject, or which any

subject estimated to be satisfactory for 8 hours. In comparison, toluene caused irritation of the eyes and throat in the majority at 300 ppm and most estimated 200 ppm as satisfactory for an 8-hour exposure.

In 1966 May [18] estimated the odor thresholds of 37 organic solvents, one of which was xylene. After measured volumes of solvent were vaporized in an evacuated 10-liter bottle, air was introduced and volunteers smelled the air at the mouth of the bottle. For xylene the odor threshold was reported as 20 ppm, with the odor of 40 ppm reported as distinctly noticeable. The odor threshold for toluene was reported as 40 ppm, with 70 ppm distinctly noticeable.

Carpenter et al [19] exposed 6 human volunteers for 10 seconds to xylene in the following sequence: 60.0, 0.0, 6.0, 0.6, 0.6, 6.0, 60.0, and 0.0 mg/cu m (these concentrations were estimated from the metered concentrations, based on previous analytical measurement data; 0.0 represents controls). This resulted in a total of 12 exposures at each level. Xylene was detected 12 times at 60.0 mg/cu m (about 14 ppm) and 8 times at 6.0 mg/cu m (1.4 ppm), but was not detected at the 2 lower concentrations. Based on these results, the most probable odor threshold was estimated to be 4.5 mg/cu m, or about 1.0 ppm.

Volunteers were also exposed [19] to measured xylene concentrations of 460, 1,000, and 2,000 mg/cu m (about 105, 230, and 460 ppm). The 15-minute exposures were limited to 1 a day to prevent buildup of symptoms. The odor of xylene was detected at each concentration by all subjects, and olfactory fatigue was reported by 3 subjects at each concentration but all reported full recovery within 10 minutes after the exposure ended. These and other effects are summarized in Table X-2. According to Carpenter et

al, [19] all of these effects were minor. The "tears" were described as increased wetness of the eyes rather than actual tearing, the dizziness was characterized as slight lightheadedness without loss of equilibrium or coordination, and the subject reporting throat irritation was not positive of the sensation. The authors concluded that 1.0 mg/liter (230 ppm) should not be objectionable to most people.

Dutkiewicz and Tyras [20] described experiments with 10 volunteers in which a known quantity of xylene was kept in contact with the skin for a measured length of time, and the residual xylene was then calculated. In this way the absorption of liquid xylene through the skin was estimated to be at the rate of 4.5-9.6 mg/sq cm/hr.

In 1965 Gusev [21] studied the effects on human volunteers of low concentrations of xylene (also benzene and toluene). In 18 subjects, the odor threshold increased in the sequence xylene, toluene, benzene. For xylene, the minimal perceptible concentration was 0.6-1.9 mg/cu m (about 0.14-0.44 ppm), and the maximal imperceptible concentration was 0.4-1.4 mg/cu m (about 0.09-0.32 ppm). To investigate the effects of each solvent on the electrical activity of the cerebral cortex, Gusev exposed 4 subjects at concentrations of solvent that were imperceptible by odor. The 4 subjects chosen were those with the lowest olfactory threshold for each solvent. Benzene and toluene were found to increase the electric potentials of the cerebral cortex, while xylene caused a marked inhibition of electrical activity. The threshold for these cortical effects by xylene was 0.32 mg/cu m (0.07 ppm), and 0.21 mg/cu m (0.05 ppm) was subliminal. Therefore 0.2 mg/cu m was recommended by this author as the "maximum permissible one-time" atmospheric concentration. Further investigations

are necessary to validate these findings.

While painting the inside of a tower with a paint containing 80% xylene and 20% methylglycolacetate, 8 workmen experienced headache, vertigo, gastric discomfort, dryness of the throat, and feelings of slight drunkenness. [22] Forced ventilation could not be used, so the painters were instructed to go outside for 10 minutes every half-hour. While cycling home from work, an 18-year-old who had been "working with paints" for 2 months suddenly felt weak and dizzy. After reaching home he had an epileptiform seizure lasting about 20 minutes. He was sent to the hospital where he suffered another seizure of much shorter duration. When examined, all reflexes were normal as was an electroencephalogram. Because there had been an instance of possibly epileptic aura in the patient at age 14, Goldie [22] suggested that organic solvents might provoke seizures in patients with latent epilepsy. No follow-up information on this patient was given.

Glass [23] described the symptoms of a man who was intermittently exposed to solvent vapors over a period of 2 months. He was examined after an acute episode of vomiting and giddiness at the end of a day's work. His appetite was poor for the following week. The solvent was 75% xylene with 25% ethylbenzene, methylethylbenzenes, and trimethylbenzenes. Concentrations of xylene in air were measured and found to be as high as 270-350 ppm at head level. However, the worker probably was intermittently exposed to much higher concentrations for 12- to 15-minute periods while he was bending over into the paint vessels he cleaned with a solvent-soaked rag.

Morley et al [24] in 1970 reported an incident in which 3 painters in a shipbuilding yard were exposed to xylene vapor in a confined space. The

concentration of xylene was later estimated to have been 10,000 ppm. After an unknown time interval, 2 of the 3 men became unconscious and therefore remained in the xylene atmosphere until they were discovered 18.5 hours later. The third man had left the tank for a period of 3 hours and then returned and also became unconscious. One of the men died shortly after discovery. At autopsy, apart from severe lung congestion with focal intra-alveolar hemorrhage and acute pulmonary edema, the victim was found to have petechial hemorrhages in the brain and evidence of anoxic neuronal damage. The other 2 men were mentally confused for some time after recovering consciousness, and both had retrograde amnesia for events preceding their loss of consciousness. There was evidence of severe impairment of renal function (a temporary severe rise in blood urea, and fall in endogenous creatinine clearance) in 1 case, but the kidneys had largely recovered by the 15th day after exposure. Both nonfatal cases showed what was interpreted as evidence of hepatic impairment (elevation of serum transaminase levels after 48 hours in 1 case to over 50 and in the other to over 100 international units, but enzyme levels then fell to within normal limits).

In 1957 Ghislandi and Fabiani [25] reported an incident of accidental ingestion of a "small amount" of liquid paint thinner composed of 90% xylene and toluene, with xylene predominating. The impurities were several acetates, but these were not identified. The day after ingestion, the urine had a specific gravity of 1.055, was positive to Fehling's test for dextrose in the urine, and contained urobilinogen. There was serological evidence (abnormal sulfobromphthalein retention) of a toxic hepatitis, but total recovery took place within 20 days. In the opinion of these authors, it could not be assumed that similar liver damage would necessarily arise

from the inhalation of xylene vapor, but they emphasized the need for liver function testing in cases of ingestion.

Joyner and Pegues [26] in 1961 described an outbreak of upper respiratory irritation with evidence of "a mild nephrotoxic action" in all of 6 men who became ill (out of a total of 8 exposed) while demolishing some epoxy-resin concrete. Substantial amounts of xylene were detected by infrared and mass spectrometric analyses of decomposition products of the concrete material and the odor of xylene was present during the demolition process. The urinary findings indicative of kidney damage were albuminuria, microhematuria, and pyuria in all 6 cases.

In 1956 Schmid [27] reviewed earlier reports of corneal disease in workers exposed to volatile solvents and discussed his own observations in furniture polishers. He reported that workers suffered eye irritation and photophobia primarily in the morning, but that these symptoms abated after a few hours of work. Slit lamp examination revealed minute vacuoles in the corneal epithelium, but the cornea healed completely in a few days with no scars remaining, even in workers who were frequently affected. Whenever the lesion occurred, workers had been exposed to a number of volatile solvents, including xylene, toluene, butyl acetate, butanol, ethylene alcohol, and ethylene acetate at unknown concentrations.

When Schmid [27] exposed 6 humans to xylene, toluene, methyl acetate, ethylene acetate, and butyl acetate evaporating from saturated filter paper, toluene was the most irritating to the eyes and xylene was the least irritating. Apparently, the exposures were not sufficient to produce corneal vacuolization in any of the humans.

Matthaus [28] described a furniture polisher who complained of burning, sensation of pressure, sensation of a foreign body, and dazzling in both eyes, with slight limitation of vision. On examination both eyes showed marked conjunctival injection, but the corneas were clear and sparkling. However, under high magnification a large number of minute, dewdrop-like vacuoles were seen in the deeper layers of the corneal epithelium opposite the palpebral fissure. The little vesicles were particularly concentrated in the pupillary and subcentral zones. Matthaus was amazed that the patient had only slight visual disturbance. The subjective eye complaints had developed within 2-3 days from the time he started working with a new lacquer solvent. Seven fellow workers were also involved but had only slight subjective eye problems. However, on ophthalmic examination, 4 of these had similar alterations in their corneas and 3 had isolated vacuole formation, despite mild subjective complaints. The cases were followed up and the corneal changes fully recovered leaving no scars after removal from exposure for an average of 8-11 days. Gas chromatographic analysis of the lacquer solvent showed it to be "practically pure" xylene. Contamination by toluene and benzene "was so minor that it could be ignored." Whether this effect is totally reversible on intermittent exposure or whether it may eventually lead to permanent damage is not known. Unfortunately no environmental data were offered as to the concentration of the xylene vapor to which these workers were exposed.

A 1957 Polish paper [29] reported troubles of heart function and electrocardiographic changes indicative of cardiac muscle damage in a 17-year-old worker who was overcome by xylene vapor. He had been exposed for an unspecified time at an unstated concentration and was unconscious for 3

hours. According to the authors, this complication was "characteristic" of the susceptibility of juveniles to the action of aromatic hydrocarbons, but they did not document this characteristic susceptibility.

In 1965 Michon [30] reported a survey of the menstrual history of 500 Polish women, aged 20-40 years, working in a shoe factory in an atmosphere contaminated by benzene, toluene, and xylene at unstated concentrations. The aromatic hydrocarbon concentrations were said to be within the Polish permissible limits (31 ppm for benzene, 67 ppm for toluene, and 58 ppm for xylene). Compared with 100 women not working in shoe production, the subjects exposed to the aromatic hydrocarbons showed some increased intensity and duration of the menstrual flow, but no alteration in menstrual rhythm. It is impossible to say which of the contaminants in the air was responsible for this influence upon menstruation, or to evaluate the significance of such menstrual disturbance.

Kucera [31] investigated the incidence of spinal malformations (sacrococcygeal agenesis, or caudal regression syndrome), in all human malformations recorded in Czechoslovakia from 1959-1966. In over 1,500,000 live and stillborn infants, more than 20,000 were malformed. Skeletal malformations included the caudal regression syndrome in 9 of these infants. Five of the 9 mothers involved had been exposed to fat solvents (xylene in 1 case) during their pregnancy. After observing teratogenic effects among chick embryos exposed to xylene vapors (discussed in Animal Toxicity), Kucera concluded that fat solvents, including xylene, may have a teratogenic effect causing caudal agenesis in man. However, his data are not adequate to support such a contention.

In 1956 Giammarinaro [32] reported a fatal case of what was described as osteosclerotic anemia with aplastic myelosis in a 46-year-old typographer. Giammarinaro gave no details of the patient's exposure except to state that he "worked since youth as a printer and had constant contacts with xylene." Without knowing the purity of the xylene or the concentration to which the man was exposed, the author considered both the bone condition and the aplastic anemia to be independent effects resulting from xylene intoxication. However, as suggested by Browning [2] in her review of this report, an alternate and reasonable explanation of the case is that the anemia was secondary to idiopathic osteosclerosis.

Lachnit and Reimer [33] described 2 fatal cases of panmyelopathy. One was in a 20-year-old girl who had been employed 1 year in a textile factory where she used an adhesive containing 27% toluene and xylene with some esters and benzene. During pregnancy she developed severe anemia, leukopenia, and thrombocytopenia. The bone marrow was generally aplastic. She died 6 weeks after the birth of a healthy child. After her death, air samples collected in the workplace revealed 8 ppm benzene and 11.1 ppm toluene, but these apparently represented an improvement over conditions prevailing during the woman's employment. No xylene concentrations were reported. In a second case, a man who had worked as a printer for 30 years was possibly acutely overexposed when a fire burned 40 liters of xylene. His health deteriorated thereafter and he died from aplastic anemia 1 year later. In an examination approximately 8 years before his death, the blood picture was essentially normal, but because his printing career had begun in 1922 there no doubt was a history of benzene exposure.

Epidemiologic Studies

Lob [34] in 1952 published a study of 19 photogravure workers, including 2 women, who had been exposed to ink-diluent vapors for periods ranging from several months to 21 years. In the 4 cases selected as being clearly pathological, the workers had been exposed for 7, 9 (a woman with intermittent exposure), 18, and 20 years. No further correlation was made between the observed abnormalities and either the degree or length of exposure. Overall results included hemoglobin levels of 70-85% in 11 subjects, including 1 of the women. The total white cell count was reported to be below 5,000/cu mm in 11 cases, below 4,000 in 1 case, and below 3,000 in 2 cases; whether this refers to a total of 11 or 14 cases is not clear. Granulocytes were below 3,000/cu mm in 9 cases, below 2,000 in 4 cases, and below 1,500 in 2 cases; whether this refers to 9 or 15 cases is unclear. Bone marrow examinations were also performed and mild general hypoplasia was found in 2 cases, severe general hypoplasia in 2 cases, and aplasia in 2 cases. In the erythropoietic series there was evidence of some hyperplasia in 7 cases and of hypoplasia in 1 case, with inhibition of maturation in 14 cases. In 15 cases the myeloid series showed inhibition of maturation. These results are suggestive of mild myelotoxicity, but once more the nature of the exposure is suspect. The ink solvent in use was described as a mixture of toluene and xylene with "no more than a minimal trace of benzene." The author stated that benzene was not used in that print shop in "appreciable quantity" except for 1 month, 5 years before this paper was published. Because of the nature of photogravure work and the previous experience in printing normally required, prior exposure to solvents had undoubtedly occurred and it seems reasonable to

suggest that there had been benzene exposure.

Sukhanova et al [35] studied 45 young to middle-aged men who manufactured xylene from gasoline. Employment ranged from 6 months to 5 years. Xylene vapor in the work atmosphere was considered to present the chief hazard, although other hydrocarbons such as gasoline were also present. The xylene concentrations ranged from 1.5-4 times the MAC in 35-40% of the samples taken, and the remainder of the air samples were below the MAC. The MAC for xylene in the USSR at that time was 50 mg/cu m (about 10 ppm). [36] Therefore, the air levels were below 50 mg/cu m in 60-65% of the samples but ranged as high as 200 mg/cu m (approximately 45 ppm). On being questioned, "approximately one-third" of the workers complained of headaches, irritability, insomnia, tachycardia, and dyspepsia. In 9 workers (20%) nervous system alterations of the type of "neurasthenic or asthenoautonomic syndromes" were established, and "autonomic-vascular dysfunction" was observed in 6 (13%). There were no other significant symptoms, and these potentially psychosomatic clinical findings were not compared with the incidence in a control population. The amount of phenols excreted in the urine was higher than normal in all cases. There were no changes in the erythrocyte, reticulocyte, or thrombocyte counts or in hemoglobin. Both the glycogen and peroxidase contents of neutrophils were found to be decreased in comparison with controls, and the decrease became more pronounced with increased duration of exposure. The authors inferred from these cytochemical changes a disturbance of the functional capacity of the leukocytes and predicted an eventual disturbance of immunologic processes.

Animal Toxicity

Chassevant and Garnier [37] observed in 1903 that toluene, ethylbenzene, and benzene, in the order of decreasing toxicity, were more toxic than xylene when administered in one intraperitoneal dose to guinea pigs. The toxic (probably meaning lethal) doses of the xylene isomers were 1.20 g/kg for p-xylene, 1.43 g/kg for m-xylene, and 1.98 g/kg for o-xylene. The toxic doses for toluene, ethylbenzene, and benzene were 0.44, 0.57, and 0.66 g/kg, respectively.

Batchelor [38] injected rats intraperitoneally and reported lethal doses of 2.0-2.5 cc/kg for xylene, 1.75-2.0 cc/kg for toluene, and 1.5-1.75 cc/kg for benzene. Xylene and toluene at doses up to 0.75 cc/kg produced no signs except apathy, but benzene at doses as low as 0.25 cc/kg produced tremor and muscular twitchings. None of these solvents had an appreciable effect on the blood counts in animals that survived the acute toxic effects.

In 1928 Smyth and Smyth [39] exposed "at least 3" guinea pigs to m-xylene vapor, initially at 450 ppm. One animal died the first day and the others were prostrate, so the exposure concentration was reduced to 300 ppm for the remainder of a total of 64 exposures. The first 2 weeks, exposures were made daily. Thereafter, animals were exposed for 4 hours a day, 6 days a week. There was "not much evidence of definite harm," although at necropsy slight degeneration of the liver and inflammation of the lungs were noted. The experiment was repeated later at 300 ppm for 58 exposures, again with few effects. Guinea pigs also were exposed to toluene and suffered no serious effects after 35 exposures at 1,000 ppm, suggesting that for this species xylene was the more toxic solvent.

Lazarew [40] reported lethal concentrations for white mice of 30 mg/liter (6,900 ppm) for o-xylene, 50 mg/liter (11,500 ppm) for m-xylene, and 15-35 mg/liter (3,450-8,050 ppm) for p-xylene. The lethal concentration of toluene was 30-35 mg/liter (8,010-9,345 ppm). These data were incorrectly cited by Browning [2] and in a Report of the International Labour Office, [41] probably because of transposition of figures from Lazarew's table. Narcotic effects were noted [40] at concentrations of 15-20 mg/liter (3,450-4,600 ppm) for o-, 10-15 mg/liter (2,300-3,450 ppm) for m-, and 10 mg/liter (2,300 ppm) for p-xylene. Exposure to m-xylene at a concentration of 15 mg/liter (3,450 ppm) resulted in the abolition of (undescribed) reflexes in the mice.

Inhalation experiments with rats and mice were described by Cameron et al. [42] Rats and mice in groups of 10 were exposed at various concentrations of toluene and to each xylene isomer. Mice appeared to be more sensitive than rats, with some mice dying after 24-hour exposures at concentrations of 2,010 ppm of m-xylene or 3,062 ppm of o-xylene. Mice survived 24-hour exposures at 4,912 ppm of p-xylene and at 6,100 ppm of toluene.

By subcutaneous injection, [42] the lethal dose in rats and mice was 5-10 cc/kg of toluene, p- or m-xylene, while the lethal dose of o-xylene was about half as large. The lethal dose for each was about half as much when injected intraperitoneally, but the relative toxicities remained the same. Although the number of animals used was not given, the authors concluded that "no definite effect" was produced when rabbits received 1-ml subcutaneous injections of o-, m-, or p-xylene on 3 consecutive days. All variations observed were considered well within the limits of normality.

Wolf et al [43] found that xylene had greater acute oral toxicity to rats than either toluene or benzene. The LD50 for xylene was 4.3 g/kg while the LD50s for toluene and benzene were 7.0 and 5.6 g/kg, respectively. Xylene and benzene caused more necrosis and were more irritating to the skin of rabbits than toluene. As indicated by the appearance, body weight, and behavior of the rabbits, these solvents apparently were not absorbed through the skin in acutely toxic amounts. Two drops of xylene instilled into rabbits' eyes produced slight conjunctival irritation with very slight and transient corneal injury, but Wolf et al [43] gave few details of the changes observed in the eyes of the rabbits.

Temporary corneal effects were also noted by Schmid, [27] who described the formation of vacuoles in the corneas of cats exposed to xylene vapor. The vacuoles reportedly disappeared within a day when exposure to xylene was stopped. The vacuoles were similar to those reported by Schmid [27] and Matthaus [28] in the eyes of furniture polishers exposed to xylene.

In a more recent study [CP Carpenter, DL Geary, written communication, April 1974] corneal vacuolization was not observed in the eyes of adult male New Zealand rabbits exposed to a mixture of xylene isomers. Xylene was instilled in the right eye of a rabbit once daily for 2 days and then 3 times daily on 3 days. Although the lids were swollen and partially denuded, the cornea appeared normal at all times on fluorescein staining and on examination by hand slit lamp and ophthalmoscope. To examine the possibility that a metabolic product might cause vacuolization, 2 rabbits were given 8 ml/kg per os and both died within 3 days. When eyes were examined with the hand slit lamp and ophthalmoscope, there was no evidence

of vacuolization prior to or following death. One rabbit was exposed at a metered concentration of 60 mg/liter (13,800 ppm) for 3 hours (the actual concentration probably was 7,000-8,000 ppm). The rabbit was prostrate after 30 minutes and the left eyelid apparently was held open against the side of the exposure chamber. Consequently, the right eye was normal but the left eye appeared rough and dry. The entire left cornea stained with fluorescein and on the following day appeared dull to the unaided eye. However, both corneas were normal within 1 week and no corneal vacuolization was seen in either eye at any time.

According to Schumacher and Grandjean, [44] the LD50s by intraperitoneal injection in mice were 1.15 ml/kg for benzene, 1.3 ml/kg for toluene, 1.4 ml/kg for a 2:1 mixture of toluene and xylene, and 1.8 ml/kg for xylene. In inhalation experiments with rats, the time in seconds of exposure to produce narcotic effects was uniformly greater for xylene than for toluene and benzene. The starting concentration in each case was 15,000 ppm. Benzene was rated in a group of substances with strong affinity for the nervous system, while toluene was in an intermediate group, and xylene was in the group with the least affinity for the central nervous system.

Hine and Zuidema [45] tested the toxicity of 10 hydrocarbon solvents representative of those used in industry. One of these was a mixture of 8-carbon aromatic solvents (the 3 xylene isomers and ethylbenzene). This sample contained at least 98% aromatics and had a boiling range of 138-141 C. The LD50 for rats when injected intragastrically was 10.0 ml/kg. By inhalation the 4-hour LC50 was 6,350 ppm, with all deaths occurring during exposure. Survivors were comatose but recovered shortly after removal from

the chamber. Rabbits were used to test for primary skin irritation, eye irritation, percutaneous toxicity, and for irritation after repeated skin applications. The xylene mixture was rated as moderately irritating and practically nontoxic by percutaneous absorption. Overall, the xylene mixture was considered by these authors to be relatively harmless under these experimental conditions.

In 1940 Rigdon [46] postulated an increase in the permeability of capillaries in rabbit skin, based on the localization of dyes, antitoxins, and carbon particles following cutaneous application of xylene. In a second paper, [47] he showed that intravenously injected staphylococci localized and concentrated in areas of skin treated with xylene. Subsequently Rigdon [48] demonstrated the localization of antibodies in areas pretreated with xylene. Finally, in 1949 Rigdon [49] reported that antihistamines did not modify the xylene localization effects, which therefore might be due to a "variation in the absorptive ability of the tissue cells" in addition to increased capillary permeability.

Falck and Moller [50] applied solvents and ultraviolet light to the shaved skin of rabbits. There was a highly significant increase in the water content of skin treated with xylene. A decrease in the catecholamines was also noted in the skin.

In 1960 Mikiska [51] and Mikiskova [52] described a technique for evaluating narcotic effects by measuring the threshold of excitability of the cerebral motor cortex. Stimulation electrodes were attached to guinea pigs, and threshold determinations were made before and after intraperitoneal injection of benzene, toluene, or xylene. Each hydrocarbon increased the excitation threshold, with the most significant elevation

caused by xylene. No change followed injection of physiological saline. Clonic muscle contractions and tremors were observed in some cases after the injection of xylene and in all cases after benzene, but not after toluene was injected. This apparently represented a second phase of action, which was accompanied by increased cortical excitability. Often the tremors and muscle contractions were observed during the narcotic state, suggesting to Mikiskova [52] that parts of the central nervous system were not subject to the same inhibition.

Battig and Grandjean [53] tested the effects of xylene exposure on avoidance conditioning in 6 experimental and 6 control rats. The conditioning stimulus was a phone buzzer, followed by an electrical shock which the rats could avoid by moving into a safe part of the cage. Experimental animals were exposed to xylene at initial concentrations of 800 ppm. Concentrations fell to 550-750 ppm in the first 2.5 hours, after which no further decrease was observed. Avoidance response tests began 2 hours after xylene exposure began. The authors observed no clear effect by xylene on any phase of the avoidance testing. There appeared to be no difference between test and control groups in acquiring the conditioned response, and in the consolidation phase the xylene-exposed animals were reported to have an insignificantly higher avoidance response rate. In the extinction phase, the exposed rats had a slightly slower extinction of the avoidance response when the buzzer was not followed by the electric shock.

Desi et al [54] investigated central nervous system dysfunction as evidenced by maze learning ability in rats given xylene. Untrained rats were injected subcutaneously either with xylene or with physiologic saline at a dose of 0.05 ml/100 g body weight. From the beginning, the xylene-

injected rats ran the maze much more slowly than the controls, and their running times declined at a slower rate. Although test scores fluctuated, the differences between test and control groups were highly significantly different in every instance. Pretrained rats were subcutaneously injected with physiologic saline (0.05 ml/100 g) or with xylene at doses of 0.02, 0.05, or 0.10 ml/100 g. Ataxia and death in experimental animals given xylene at 0.10 ml/100 g led to discontinuation of experiments at that level. The rate of weight gain was reduced compared to controls and the running times for the xylene groups were longer, but the differences were not statistically significant. Thus, the ability to learn a maze seemed to suffer more than the ability to perform trained behavior.

Investigating the role of irritation in carcinogenesis, Berenblum [55] exposed white mice to 3,4-benzpyrene with xylene, and to xylene alone as a control. Berenblum concluded that the addition of xylene did not produce a significant difference in the yield of tumors. He also concluded that xylene was probably not carcinogenic, although one minute tumor (which regressed) was observed in a control animal treated with xylene. Xylene applied at a concentration which produced irritation similar to that produced by croton oil showed no evidence of being co-carcinogenic.

In experiments by Pound and Withers, [56] mice received daily right-side subcutaneous injections of 0.25 ml of xylene from 1-6 days prior to injection of 25 mg urethane. Seven days following urethane injection, and once a week thereafter, the entire back of each mouse was painted with 0.25 ml of croton oil in acetone (0.5% solution). The numbers of survivors and the number and location of papillomata were counted each week for 20 weeks. Xylene showed some toxicity, as 8 mice died within 2 weeks. Groups of mice

treated with xylene gave significantly ($p = 0.005$) higher yields of left-sided tumors than mice treated with acetic acid, trichloroacetic acid, turpentine, or scarification. The relative severity of changes in the skin produced by the various irritant substances correlated with the increases in tumor yield observed in animals treated with these substances. The authors concluded that, in addition to a local influence, xylene and some other substances "appeared to have a general effect that influenced the tumor yields." Pound [57] reviewed this work and commented that the augmenting effect was not related to carcinogenic or promoting properties but to the inflammation and hyperplasia produced in the skin. This seems to be a more reasonable explanation.

In 1970, Pound [58] described further experiments using ultraviolet light to attempt to initiate tumor formation in mice. Single short exposures did not produce tumors, but tumors developed when the exposure was followed by application of croton oil. Ultraviolet light apparently was acting as an initiator. If the skin of experimental mice was pretreated with xylene, acetic acid, or croton oil before irradiation, then the number of tumors increased. Pound concluded [58] that cells which had been induced to proliferate were more susceptible to induction of tumors by ultraviolet light than normal cells.

Experiments by Jellinek were reported by Kucera in 1968. [31] The possible implication of fat solvents as etiological agents in human sacral agenesis led to experiments in which chick embryos were exposed at an unstated concentration of xylene vapor for 60-240 minutes. A significant increase in malformations and mortalities was observed, and this correlated positively with the length of exposure to xylene. Younger chick embryos

were more susceptible. The author concluded that xylene had a teratogenic effect. [31] In view of the results of Kucera's survey of human sacrococcygeal agenesis, this seems to be an effect, if real, of fat solvents in general, rather than of xylene in particular.

To investigate possible embryotoxic or teratogenic effects, Krotov and Chebotar' [59] exposed pregnant white rats to dimethylterephthalate, "paratoluic methylate (PT-ether)" (apparently this was methyl (p-toluic acid) ether), or p-xylene vapor during gestation. Twenty-nine rats were exposed to p-xylene at 500 mg/cu m (115 ppm) for 20 days, 24 hours a day. On the 20th day of pregnancy, the experimental and 17 control rats were killed. A count was made of corpora lutea in the ovaries, the number of implantation points, and the number of living and dead fetuses. Fetuses were examined grossly and microscopically for abnormalities. Experimental rats experienced significantly greater preimplantation mortality (32.1%) than controls (11.3%). Postimplantation mortality was also higher (38.9% vs 4.8%). No teratogenic effects were observed, the only malformed fetus (shortened tail and adactylia of the 5th toe of a rear foot) being 1 of 110 living fetuses in the "PT-ether" group.

Kashin et al [60] in 1968 exposed 9 chinchilla rabbits at 200 mg/cu m (46 ppm) for 2 hours daily, and a second group of 9 was exposed at 50 mg/cu m (12 ppm) for 4 hours daily, both groups for 10-12 months. They suggested 3 periods of change due to long-term action by small concentrations of xylene. The first, or compensation period of 1-3 months, was characterized by increases in hemoglobin content, erythrocytes and leukocytes, increases in common proteins and especially in gamma globulins, increased activity of blood acetylcholinesterase, and increased excretion of 17-ketosteroids in

urine. At the same time, inhibitory effects were exhibited by weight loss and by decreased immunological response. A second or normalization phase then occurred during the 4th-8th months of exposure. The authors interpreted the changes to indicate weakening of adrenal cortex functions, disturbance of intermediary metabolism, and decreased immunobiological activity, and they concluded that these reflected overstraining of defense mechanisms and adaptation systems. The final or physiological decompensation phase occurred with decreases in the activity of several systems. The authors concluded [60] that more pronounced changes were caused by a long exposure to a low concentration of xylene than by shorter exposure to a higher concentration. They considered a concentration of 50 mg/cu m (12 ppm) with 4 hours daily exposure to be an unacceptable exposure limit. It is difficult to evaluate the significance of these findings in light of an inadequate description of the experiment, including results in control animals.

Batchelor [38] exposed rats to benzene, toluene, xylene, or high-flash naphtha by inhalation, subcutaneous injection, or intraperitoneal injection. This work was supported by the National Safety Council, who also published the results, [61] and it was reviewed and discussed by Winslow. [62] In the inhalation experiments, rats were exposed for 18-20 hours a day at various concentrations of solvent vapor. Batchelor did not report analyzing the xylene for benzene contamination, but the boiling point of the xylene used was 139 C, suggesting that there probably was little benzene present. Of 4 rats exposed to xylene at 1,600 ppm, 1 died after 2 days and 1 after 4 days. The remaining 2 were removed after 2 days of exposure and recovered. [61] Initial signs of exposure were instability

and incoordination with evidence of mucous membrane irritation. Narcosis prevented ingestion of food and water, leading to weight loss, anhydremia, and death. The white blood count was reduced by 27% in the rat that died after 4 days of exposure. There was no effect on the white count of rats exposed only 2 days. An increased red blood cell count was attributed to the anhydremia. Four rats exposed at 980 ppm for 7 days exhibited similar signs but narcosis did not result. The bone marrow and spleen were hyperplastic and kidneys showed acute congestion with moderate cloudy swelling but no signs of an acute nephritis. One rat had a 32% reduction in the white count. No signs of toxicity were observed in 8 rats exposed at 620 ppm for 7 days, with the exception of a 30% reduction in the white count of 1 rat. In contrast, benzene at high concentrations (1,000-2,440 ppm) did not produce narcosis and death, but after 6-7 days of exposure the rats' skeletal muscles became hypertonic and rats suffered clonic spasms and a spastic gait. This condition persisted for 3-4 days after exposure ended. Leukopenia and destruction of the bone marrow bordering on aplasia were observed after exposure at all benzene concentrations used (2,440, 1,035, 815, and 460 ppm). [38,61,62]

Mixed in equal volumes of olive oil, the solvents were also injected subcutaneously. [38] Xylene was injected for 10 consecutive days at doses of 1 and 2 cc/kg. This resulted in slightly reduced activity and a transient reduction in the red blood cell count, but had no effect on the white blood cell count. At autopsy, the bone marrow was found to be hyperplastic, and mild necrosis of the liver and diffuse nephritis were seen. Benzene at a dose of 1 cc/kg caused a reduction in the white count to below 2,000/cu mm after 4-21 daily injections. A reduction in the red blood cell

count appeared later, accompanied by bone marrow aplasia. General signs, which appeared early and became progressively more severe as benzene injections continued, included apathy, extreme weight loss, great weakness, and tonic and clonic muscle contractions of the body and extremities.

In 1924 Woronow [63] reported experiments in which he injected rabbits subcutaneously twice daily with benzene in olive oil at a dose of 1.5 ml (units are assumed since none were given in the article). Leukopenia developed rapidly, and a leukocyte count of zero reportedly was observed after 9-11 days. When xylene in olive oil was injected subcutaneously in the same dosage, the leukocyte count dropped in the first 4-5 days then rose markedly to 20,000-30,000 by the 9th or 10th day. The elevation was due primarily to increased numbers of monocytes and neutrophils. Myelocytes and juvenile forms were not observed. By the 5th day, the granules of neutrophils were reported to be exclusively basophilic, and monocytes reportedly began to show basophilic granulation. Bone marrow was hyperplastic. Similar results were observed after rabbits were injected with toluene. Cumene produced a less pronounced leukocytosis with a shift to the left. Woronow [63] concluded that the methyl groups acted on leukocytes and on the hematopoietic organs, and suggested that increasing the number of methyl groups on the benzene ring produced changes increasingly similar to myeloid leukemia, but it seems more likely that these changes in xylene-treated animals were a normal response to toxic insult.

Farber [64] in 1933 reported similar experiments that had been conducted to verify Woronow's [63] findings. After rabbits were subcutaneously injected twice daily with 1.5 ml xylene in olive oil, there

was an immediate reduction in the white count, followed by an increase to about 60% above the initial values. No increases as high as those reported by Woronow were observed. Farber noted that the same initial drop in leukocytes occurred when a rabbit was injected with olive oil alone. The responses after xylene injections were summarized as a definite leukocytosis, a shift to the left, monocytosis, atypical cells in the granulocyte series (similar to a degeneration), disturbed red cell analysis (polychromasia and increased numbers of normoblasts), and hyperplasia of the bone marrow.

Because injection of xylene caused necrosis which led to the skin sloughing off in patches, Farber [64] exposed rabbits to xylene by inhalation to rule out effects due to irritation, infection, and necrosis. Rabbits were placed in a bell jar, with xylene evaporating from a filter paper, until they were unconscious. In this case there was no leukocytosis, shift to the left, or monocytosis. Changes in the red blood series were similar to those observed after injections, but were much less severe. The bone marrow was not hyperplastic. Farber therefore concluded that the skin irritation and severe inflammatory processes were responsible for the blood changes observed in the injection experiments. The possibility of benzene contamination is an additional factor that complicates the interpretation of these studies reported in 1929 by Woronow, [63] and in 1933 by Farber. [64]

Engelhardt [65] exposed cats and rabbits at xylene concentrations of 10 mg/liter (2,300 ppm) and 25 mg/liter (5,750 ppm), and observed a reduction in the number of red blood cells and a pronounced leukocytosis. After cats and rabbits were injected with xylene, Engelhardt saw a distinct

shift to the left and leukocytosis, but like Farber [64] he attributed these changes to local effects such as inflammation and necrosis at the injection site. Engelhardt concluded that toluene and xylene were less toxic than benzene.

Fabre et al [66] exposed rats and rabbits for 8 hours a day, 6 days a week to a benzene-free mixture of the xylene isomers. Six rabbits were exposed at 5 mg/liter (1,150 ppm) for 40-55 days, and 12 rabbits and 9 rats were exposed at 3 mg/liter (690 ppm) for 110-130 days. At 3 mg/liter there were no significant changes in the blood. At 5 mg/liter there were decreases in both red and white cells. At both concentrations of xylene the bone marrow was hyperplastic, but there was no tendency to aplasia. Microscopic examination revealed vascular congestion in the liver, kidney, heart, adrenals, lungs, and spleen of animals exposed at each concentration. The renal lesions (chronic subacute glomerulonephritis) were observed after exposure at both concentrations and were considered the most important observations. Based on this observation, the authors recommended caution in the use of xylenes, and suggested that such effects in man would be indicated by an increase in blood urea and the appearance of albumin and blood in the urine.

In 1968, Speck and Moeschlin [67] were unable to demonstrate any myelotoxic effects in rabbits from toluene or xylene. Rabbits received toluene or xylene subcutaneously in doses of 300 mg/kg/day for 6 weeks or 700 mg/kg/day for 9 weeks. Erythrocyte, reticulocyte, leukocyte, and thrombocyte counts were made twice weekly, and all values fluctuated within normal limits. Cytopenia was not induced in any cell type. Using tritiated methyl thymidine and autoradiographic techniques, the authors

determined that neither toluene nor xylene affected DNA synthesis in the bone marrow. Earlier, similar experiments with benzene had resulted in aplastic anemia, and autoradiographic analysis had demonstrated arrested DNA synthesis in the bone marrow. [68,69] The authors suggested [67] that earlier reports of aplastic anemia caused by toluene or xylene could be attributed to benzene contamination, and stated that their results presented "a substantial argument for the lack of myelotoxicity of toluene and xylene."

In 1970, Jenkins et al [70] reported the results of long-term inhalation studies of benzene, toluene, and o-xylene using rats, guinea pigs, monkeys, and dogs. Pre- and postexposure body weight, hematologic data, and mortalities were reported. Experiments with o-xylene were conducted at 3,358 mg/cu m (770 ppm) and 337 mg/cu m (78 ppm), while studies with toluene were conducted at 4,095 mg/cu m (1,085 ppm) and 389 mg/cu m (105 ppm). With benzene, exposure levels were 817 mg/cu m (255 ppm) and 98 mg/cu m (30 ppm). At the higher concentration in each case, there were 30 repeated exposures for 8 hours a day, 5 days a week, while at the lower concentration there was continuous exposure for 90 days. Animals were also continuously exposed to benzene at a concentration of 56 mg/cu m (17 ppm) for 127 days. At the end of the exposures, animals were killed and necropsied. Sections of heart, lung, liver, spleen, and kidney were taken from all species; sections of brain and spinal cord were obtained from dogs and monkeys for microscopic examination. Results of microscopic examinations were negative and no significant changes were noted in body weight or hematologic data. However, the authors reported only leukocyte counts rather than complete differential white blood counts and they did

not examine the bone marrow, so these results are not negative evidence of benzene effects.

In 1974 Carpenter et al, [19] using a solvent sample containing 80.5% mixed xylenes (65.0% m-xylene) and 19.3% ethylbenzene, exposed male rats and dogs at measured concentrations of 3.5, 2.0, and 0.77 mg/liter (805, 460, and 175 ppm) for 6 hours a day, 5 days a week for 13 weeks. Blood analyses (including hematocrit, total erythrocyte count, reticulocyte count, total and differential leukocyte counts, serum alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxalacetic transaminase, and blood urea nitrogen) were determined initially, at intervals during exposure, and at the end of the exposure period. Rats were killed at intervals and all surviving rats and dogs were killed at the end of 65-66 exposure days. No gross or microscopic lesions were ascribed to inhalation of the mixed xylenes. Blood counts and blood analyses likewise did not differ significantly from baseline levels or from levels in unexposed controls.

Using serum ornithine carbamyl transferase (OCT) activity to screen for liver damage, DiVincenzo and Krasavage [71] injected guinea pigs intraperitoneally with organic solvents and collected blood samples 24 hours later. In 117 control animals, serum OCT activity averaged 2.0 ± 1.6 international units (IU), but after injection with 1,000 mg/kg of xylene, the OCT activity of 4 guinea pigs averaged 18.4 IU. At a dose of 2,000 mg/kg, 3 of 4 animals died, and mean OCT activity was reported as 25.2 IU. As a positive control, carbon tetrachloride was administered in doses of 5-150 mg/kg. The OCT activity in the 5 mg/kg group was 3.8 IU, and in the other groups (25-150 mg/kg) ranged from 37.1-64.4 IU. Liver sections from

each test animal were examined microscopically, and showed signs of lipid deposition in the hepatocytes at both xylene dosages, but no evidence with hematoxylin-eosin stain of hepatocellular damage.

Many of these studies of xylene have examined its toxicological properties in comparison with those of benzene or toluene. Reports regarding the relative toxicity of the isomers of xylene and toluene and benzene are conflicting. Smyth and Smyth [39] and Wolf et al [43] published results suggesting that xylene was more toxic than toluene. The data of Chassevant and Garnier, [37] Batchelor, [38] and Schumacher and Grandjean [44] showed the opposite. The work of Lazarew [40] and of Cameron et al [42] indicated that toluene was less toxic than some but more toxic than other xylene isomers, but these papers did not agree in detail. No clear pattern emerges from these studies, and it is only possible to conclude that the acute toxicity of xylene is of the same order of magnitude as that of toluene. This does not necessarily reflect the relative chronic toxicities.

Changes in the blood [38,64] and hyperplasia of the bone marrow [38,64,66] have been reported in animals injected subcutaneously with xylene. Leukocytosis and a reduced red count were reported in a 1935 inhalation study. [65] However, blood changes were not seen in 1 of these older studies when the animals were exposed to xylene by inhalation, [64] and the author attributed, probably correctly, the blood changes seen after injection to the expected response to inflammatory processes. More recent studies have shown no blood changes after exposure by inhalation [19,66,70] or by injections. [67] In contrast, benzene has produced aplasia after subcutaneous injection [68,69] and after inhalation. [38]

Correlation of Exposure and Effect

Like most organic solvents xylene has irritant effects on the skin, [2,3,72] and on the mucous membranes, [24] including the conjunctiva [28] and respiratory tract. [24] Xylene also has narcotic effects on the central nervous system, [21,24] variable effects on the liver [12,24,25] and kidneys, [24,26] and rather nonspecific, probably irritant, effects on the gastrointestinal tract. [22,23] Questionable effects on the cardiovascular system [12,29] and female reproductive endocrine system [30] have been reported. In the past, xylene was thought to have significant deleterious effects on the bone marrow and hemopoietic system in general, [10,12-15] but in the light of more recent research, this appears doubtful. [19,66,67,70] The better controlled studies of Speck and Moeschlin [67-69] give strong support to the conclusion that xylene uncontaminated by benzene does not have such effects.

The narcotic and other effects of xylene at high concentrations were well established by the incident described by Morley et al. [24] Three painters working in the confined space of a ship's fuel tank were overcome by xylene vapor from the paint they were using, in which the solvent was 90% xylene. The authors estimated that the xylene concentration had reached 10,000 ppm. It was not known how long it took the men to lose consciousness, because they were not found until 18.5 hours after they entered the tank. One died shortly after discovery and at autopsy showed pulmonary edema and intra-alveolar hemorrhages. The other 2 men survived and recovered completely in about 2 days. They both had temporary hepatic impairment (inferred from elevated serum transaminase levels) and 1 had evidence of temporary renal impairment (increased blood urea and reduced

endogenous creatinine clearance).

Giddiness, anorexia, and an episode of vomiting were observed in a paint-pot cleaner who used a solvent containing 75% xylene (the remaining 25% consisting of ethylbenzene, methylethylbenzenes, and trimethylbenzenes). [23] At head height above the paint-pots, the xylene concentration ranged from 60-100 ppm when the pots were cold but from 270-350 ppm when the pots were warm. It was believed that the worker was exposed frequently to an even higher level when he placed his head inside the warm pots during cleaning.

Nelson et al [17] exposed a group of volunteers, usually 10, of both sexes to various solvent vapors, including xylene, in an exposure chamber for 3-5 minutes. The subjects were questioned about the subjective effects of eye, nose, and throat irritation. They were also asked the highest concentration which they considered satisfactory for an 8-hour exposure. The majority of subjects found a xylene concentration of 200 ppm irritating to eyes, nose, and throat and judged 100 ppm to be the highest concentration subjectively satisfactory for an 8-hour exposure.

In a Soviet xylene extraction plant, xylene concentrations were below 50 mg/cu m (about 10 ppm) in 60-65% of the air samples taken, and ranged from 75-200 mg/cu m (about 15-45 ppm) in the remaining samples. [35] Forty-five workers had been exposed for periods ranging from 5 months to 6 years. [35] One-third of these workers complained of occasional headaches, insomnia, irritability, tachycardia, and dyspepsia. If any were made, similar observations were not reported for unexposed workers. What were called neurasthenic or asthenoautonomic syndromes were observed in 9 workers (20%) and autonomic-vascular dysfunction (not further defined) was

observed in 6 workers. Again there were no similar observations in a control group. The amount of phenols excreted in the urine was higher than normal in all cases (the actual amount and the "normal" were not given). Peripheral blood polymorphonuclear leukocytes had a decreased glycogen and peroxidase content, compared with unidentified controls. These decreases were more marked in those employed 3-5 years than in those employed 1-3 years. The authors projected that such cytochemical changes might eventually lead to disturbance of the immunological processes.

In the first 30-40 years of this century a variety of blood changes, including aplastic and pseudopernicious anemia, were attributed to xylene exposure. [10,12-15] However, because the xylene of that era was contaminated with benzene and other hydrocarbons, [9,15,16] these reports can be regarded only as evidence that a health problem existed at that time. More recent studies that have reported blood changes in exposed workers have involved known exposure to benzene as well as xylene [33,34] or employment in a print shop during the time when benzene contamination of xylene was probable. [32-34] In animal experimentation, changes in the blood and bone marrow have been reported after injections of xylene [38,64] and in a 1935 study [65] after inhalation. More recent studies do not report blood changes after injections [67] or after exposure by inhalation, [19,66,70] and studies [67-69] with good controls strongly support the conclusion that uncontaminated xylene does not have myelotoxic effects.

In 1950 Browning [73] called xylene "innocuous to the haematopoetic system." In a 1965 review, [2] she pointed out what she considered to be the dubious nature of practically all the reports of bone marrow effects since the exposures described were either admitted to involve concomitant

exposure to benzene, or were suspected of involving significant amounts of benzene as a contaminant. In a series of papers reviewing available data and presenting his own results, Gerarde [3,72,74,75] reviewed the evidence and concluded that the myelotoxic properties of benzene were destroyed by alkylation of the benzene ring. Lehmann and Flury in 1943, [76] Johnstone and Miller in 1960, [77] and Lederer in 1972 [78] all expressed the view that there was little or no evidence that xylene was a myelotoxicant.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Sampling and Analysis

Xylene can be directly measured in the field with a calibrated combustible gas indicator, [72,79] but the method is nonspecific, being subject to interference in the presence of other organic compounds. The same disadvantage applies to the interferometer. [1,72] Detector tubes also offer a rapid, simple procedure, but depend upon an estimation of the length of a stain produced in the tube or on the intensity of color produced. Unfortunately, detector tubes are not particularly accurate, and are also nonspecific, other aromatic hydrocarbons also producing colors. [80-82]

Collection in a bubbler containing sulfuric acid and formaldehyde has also been proposed, but this method is little more than semiquantitative. [83,84] Collection in a bubbler containing methanol with subsequent measurement by ultraviolet spectrophotometry has been described, [85] but has the disadvantage of requiring that the sampling unit be placed in dry ice to prevent evaporation. In addition, sampling of breathing zone exposures is more difficult with sampling devices containing liquids.

Silica gel has been used by a number of investigators to collect xylene vapor for laboratory analysis. [86-88] In the presence of water vapor, however, there may be considerable loss. Whitman and Johnston [89] reported that this problem could be overcome by the use of a molecular sieve prefilter.

Plastic bags have also been used to collect xylene and other organic vapors. [90-92] Possible losses with time through reaction of the specific compound with the type of plastic used must be determined in advance.

Adsorption of xylene vapor on activated charcoal has been studied by a number of investigators. [93-95] Activated charcoal is the preferred sampling method since the xylene is not displaced by water vapor, as is the case with silica gel, and because it is a simpler, more convenient procedure than the use of plastic bags or bubblers. White et al [95] have defined the design of activated charcoal tubes suitable for sampling occupational exposures to xylene, and such tubes are commercially available. They reported average desorption efficiencies (percent xylene recovered from the charcoal) of 94% (range 91-96%) for 100 ppm concentrations of xylene sampled alone and 98% (range 97-100%) in the presence of 6 other organic vapors.

Various methods for analyzing the collected samples have been used, including colorimetric, [83,84] infrared analysis, [88] and ultraviolet spectrophotometry. [85,87,96] In recent years, however, gas chromatography has become the method of choice of most investigators for analysis of organic solvents. [86,88,89,93-95,97-99] Gas chromatography also offers suitable specificity and sensitivity. [89,93,95]

Appendices I and II present recommended methods for sampling and analyzing xylene. These include collection of personal samples, using charcoal tubes, desorption with carbon disulfide, and measurement with a gas chromatograph equipped with a flame ionization detector. [94,95,100] The sampling method has the advantages of using a small, portable sampling device and of involving no liquids. Analysis is by means of a quick

instrumental method that can be used for the simultaneous analysis of 2 or more solvents in the same sample. Disadvantages include the fact that the amount of sample that can be collected is limited by the number of milligrams that the tube will hold before overloading, and the fact that volatile compounds can migrate to the backup section during storage before analysis. The precision of the method is limited by the reproducibility of the pressure drop across the charcoal tubes. Nevertheless, the accuracy of the overall sampling and analytical method is 10%. [100,101] Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions.

Control of Exposure

Engineering design and work practices for xylene should have, as their main objectives, controlling vapor concentrations, minimizing skin contact, and preventing fires.

Closed systems, properly operated and maintained, should be used, where practicable, to achieve all 3 of these objectives. Where closed systems are not feasible, well-designed local exhaust ventilation should be provided. [6] Guidance for design can be found in Industrial Ventilation--A Manual of Recommended Practice, [102] or more recent revisions, and in ANSI Z9.2-1971. [103] Exhaust air should not be recirculated, and should be scrubbed to prevent pollution of the outdoor air. Respiratory protective equipment is not an acceptable substitute for proper engineering controls, but should be available for emergency purposes, and for nonroutine maintenance and repair situations.

Sparkproof equipment in exhaust hoods, stands, booths, or similar

arrangements should be employed where xylene-containing paints or lacquers are sprayed. Exposures should be minimized by isolating painting and drying areas.

Protective clothing should be worn wherever required to prevent skin contact. Equipment made of natural rubbers should be avoided since it is subject to solvent action by xylene. Neoprene or other materials resistant to xylene should be used for gloves, aprons, or other protective clothing. [8]

Xylene is a flammable liquid that vaporizes at normal temperature. At 25 C, the vapor pressures of the isomers range from 5.2 mm Hg for o-xylene to 8.6 mm Hg for p-xylene, and the lower explosive limit is 1.1% by volume. [1] The vapor can travel a considerable distance to a source of ignition and flash back. Ignition sources include open flames, chemical reactions, lightning, smoking, hot surfaces, radiant heat, and spontaneous combustion. Static electricity can also present a hazard. [8] All metal dispensing containers should be properly grounded when pouring.

Structures and operations should be designed with the objectives of reducing the possibilities of fires, and of limiting the size or spread of any which might occur. Storage of materials is also an important factor. Firefighting procedures should be developed in advance, and local fire departments, as well as plant employees, should be informed of the hazards involved. [8]

Biologic Evaluation

The first report on xylene metabolism apparently was that of Schultzen and Naunyn [104] in 1867. They demonstrated toluric acid (the

glycine conjugate of toluic acid) in the urine of dogs and men after ingestion of xylene. In 1892, Curci [105] reported that xylenols were also formed as metabolites of xylenes. This was confirmed in 1914 by Filippi, [106] who also showed that the ortho isomer had greatest chronic toxicity in the dog.

Bray et al [107] investigated the metabolism in rabbits of the xylene isomers, administered by stomach tube. They reported that all 3 isomers were primarily oxidized to the corresponding toluic acid (60%, 81%, and 88% of the administered dose, respectively, for o-, m-, and p-xylene). The o-toluic acid was excreted mainly unconjugated and as an ester glucuronide, with a small amount excreted as a glycine conjugate. The m- and p-toluic acids were excreted chiefly as glycine conjugates with only small amounts excreted free or conjugated with glucuronic acid. There was some evidence of hydroxylation: 6% of o- and 4% of m-xylene doses were excreted as ethereal sulfate and 10-15% of the p-xylene dose was probably excreted as an ether glucuronide. Additionally, there was some evidence that p-xylene may have given rise to a xylenol.

In a later paper, Bray et al [108] presented additional data on the fate of xylenes and xylenols in the rabbit. They concluded that it seemed most likely that the phenolic material excreted after the administration of xylenes consisted mainly of xylenols, both free and conjugated. When the xylenols were administered directly to rabbits only small amounts of further oxidation or hydroxylation products were detected. The authors considered this evidence that the amount of the xylenols formed from the metabolism of xylene was probably very small.

Fabre et al [109] administered pure xylene isomers to rabbits, rats, and guinea pigs by stomach tube. Their results confirmed the oxidation of each isomer to the corresponding toluic acid and indicated that the second methyl group resisted oxydation, since no phthalic acids were isolated. In the case of o- and p-xylene, the phenolic metabolites were identified as 3,4-dimethylphenol (asymmetrical o-xylenol) and 2,5-dimethylphenol (p-xylenol), respectively. A xylenol metabolite of m-xylene was isolated but not identified.

Bakke and Scheline [110] administered each of the 3 xylene isomers to rats in an oral dose of 100 mg/kg body weight, and phenolic metabolites were quantitatively estimated in hydrolyzed urine samples by gas chromatography. o-Xylene was metabolized to 3,4-dimethylphenol (0.1% of the dose) and to very small amounts of 2,3-dimethylphenol (approximately 0.03% of the dose). m-Xylene was metabolized to 2,4-methylphenol (0.9% of the dose), and p-xylene to 2,5-dimethylphenol (1.0% of the dose). In addition, 2-methyl benzyl alcohol was a metabolite of o-xylene. This had not been previously reported. This work confirmed the earlier work of Bray et al [107] suggesting oxidation of a methyl group to give toluic acids as a major pathway for xylene. Bakke and Scheline [110] noted that the conversion of aromatic hydrocarbons to phenols by hydroxylation "is accompanied by an appreciable increase in acute toxicity," but they considered this of little importance because the metabolites occurred in small quantities which were partly eliminated as glucuronides and ethereal sulfates.

Fridlyand [111] injected guinea pigs and rats subcutaneously with 90 mg doses of benzene, toluene, o-, m-, or p-xylene, then collected urine for

analysis. According to Fridlyand, toluene and xylene were demethylated and phenol was formed. In rats, the quantity of phenol excreted was greatest after injection of benzene and decreased in the order p-xylene, toluene, m-xylene, and o-xylene. The relationship was the same for guinea pigs except that o- and m-xylene, in that order, resulted in the least phenol.

Recent quantitative inhalation experiments by Ogata et al [112] showed that 72% of absorbed m-xylene was excreted in the urine of male volunteers as m-methylhippuric acid during and within 18 hours after the end of exposure. Attempting to relate excretion data to exposure levels, the authors found that total excretion during and for 18 hours after exposure was most accurate, followed by excretion rates (in mg methylhippuric acid/minute) during exposure. Least accurate but still useful were urine concentrations of methylhippuric acid, corrected to a specific gravity of 1.024, during the afternoon and morning exposure periods. Concentrations uncorrected for specific gravity were too variable to be of use.

Subjects were exposed in groups of 4 or 5 for 7 hours, with a 1-hour break after the 3rd hour, to m- or p-xylene at 100 ppm, or to m-xylene at 200 ppm. [112] Urinary excretion of methylhippuric acid rose during exposure, peaking 6-7 hours after exposure began. The results are summarized in Table X-3. Based on these results, the authors proposed "screening levels" 2 standard deviations below the average excretion after exposure at 100 ppm. They suggested that if methylhippuric acid excretion by an exposed worker was above the screening level, it should be taken as evidence that the person might have been exposed above 100 ppm (according to their statistical interpretation, this would be true in 5% of the cases). Separate screening levels were given for samples taken in the

morning and afternoon, as well as a screening level for the rate of excretion over a 7-hour exposure period. These proposed screening levels are given in Table X-4.

This report by Ogata et al [112] contains the only published data found by NIOSH that quantitatively correlate the urinary excretion of xylene metabolites with exposure levels. Unfortunately, this work was done using pure m- or p-xylene. Thus, there are no data correlating urinary excretion with o-xylene exposure, and the excretion resulting from exposure to mixed xylene isomers is unknown. If mixtures do not alter the relative metabolism and excretion of the isomers, it is possible that the excretion of, for example, m-methylhippuric acid could be used to compute total xylene exposure based on the percentage composition of the mixture in use. The suitability of this procedure has not been verified experimentally.

Ogata et al [113] also developed 2 analytical procedures for the determination of m- and p-methylhippuric acid in urine, based on colored azlactone formation. A silica gel method involved extraction of the methylhippuric acids with an ethyl ether/ethyl alcohol solution, drying with silica gel, and azlactone formation using p-dimethylaminobenzaldehyde in acetic anhydride. The azlactones were extracted with ethyl ether and the absorbance read at 460 nm. Standard solutions prepared by the same extraction procedure were applied to aqueous solutions of m- or p-dimethyl-aminobenzaldehyde reagent and gave a positive reaction with urea. However, the extraction procedure using ethyl ether/ethyl alcohol did not extract urea from urine. The sensitivity of this method was 4 μg/ml urine. The other method, using benzenesulfonyl chloride, was less sensitive (20 μg/ml urine), but was much simpler to use. The methylhippuric acids were

extracted with ethyl acetate or ethyl ether/ethyl alcohol solution and the azlactones formed by reaction with benzenesulfonyl chloride in pyridine solution. The absorbance was then read at 380 nm against a pyridine-benzenesulfonyl chloride blank. Recoveries by both methods were 94-100%. Hippuric acid, a urinary metabolite of toluene, is also determined by both methods, but hippuric acid, m-, and p-methylhippuric acid can be separated by paper or thin-layer chromatography and then determined spectrophotometrically.

A more recent paper by Buchet and Lauwerys [114] described a gas chromatographic technique for the determination of both hippuric acid and m-methylhippuric acid in urine. Comparison indicated that this technique was as specific and as sensitive as that reported by Ogata et al, [113] but it was much more rapid. A known amount of heptadecanoic acid, as the internal standard, was added to urine before its extraction with ethyl acetate. After evaporation of the solvent, the acids were methylated with diazomethane and the residue was taken up in methanol and injected into the gas chromatograph. The ratio of the height of the m-methylhippuric acid peak to the height of the heptadecanoic acid peak was calculated and by reference to a calibration curve prepared in the same conditions the urine concentration of the acid was determined. This technique could simultaneously determine both hippuric and m-methylhippuric acid, but was not described in connection with the metabolites of o- and p-xylene. Therefore, while this method seems promising, its applicability to mixtures of o-, m-, and p-methylhippuric acid is unknown.

These reports indicate that the major metabolic pathway for xylene involves oxidation of a single methyl group followed by conjugation with

glycine or glucuronic acid. [104,105,107,109,112] The relatively low toxicity of these major metabolites was cited in reviews by Laham [115] and Gerarde [75] as an explanation for the apparent lack of myelotoxicity on the part of xylene and other alkylbenzenes. In review articles, Browning, [2] Laham, [115] and Gerarde [75] have attributed the myelotoxicity of benzene to its phenolic metabolites. However, as pointed out in the recent NIOSH benzene criteria document, [116] the phenolic metabolites do not produce hematopoietic toxicity when administered directly. In any event, while some hydroxylation of xylene apparently occurs, [107-110] the amount of phenolic metabolites produced is small. [109,110]

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The earliest US standard for xylene appeared in a list of toxic limits published in 1943, [117] in which the value of 200 ppm was recommended as a Maximum Allowable Concentration (MAC). In 1945 Cook, [118] in his then comprehensive list of recommended MACs, cited 200 ppm for xylene in all the states mentioned (California, Connecticut, Massachusetts, New York, Oregon, Utah) as well as for the USPHS and the "American War Standard." This MAC was established by analogy with toluene, but Cook commented that "xylene vapor is somewhat more irritating to the eyes than that of toluene and it is probable that a somewhat lower limit of exposures may be required to permit comfort of the worker." [118]

In 1946, the American Conference of Governmental Industrial Hygienists (ACGIH) recommended a MAC of 200 ppm for xylene. [119] In 1948 the terminology was changed to Threshold Limit Value (TLV), but the level remained at 200 ppm. According to the 1962 documentation, [120] the effects of xylene were considered to be similar to those of toluene. The 200 ppm TLV was based on the report by Nelson et al [17] of irritation at 200 ppm and on the suggestion of Greenburg and Moskowitz. [121] In 1963, the ACGIH for the first time added a "C" (ceiling) notation to a number of TLVs, including that for xylene. [122] This 200 ppm ceiling remained in effect until the TLV was changed to a time-weighted average (TWA) of 100 ppm, proposed in 1965 [123] and adopted in 1967. [124] The basis given in the 1966 [125] and 1971 [126] documentation was Gerarde's opinion [3] that 100 ppm would be more acceptable from the standpoint of comfort and worker

performance, as well as the report by Nelson et al [17] of irritation at 200 ppm. The current TLV remains a TWA of 100 ppm, except that in 1974 the "Skin" notation was added, [127] which was intended to suggest the need to prevent skin absorption.

In 1951 Elkins [128] listed the maximum allowable concentration (presumably for Massachusetts) as 150 ppm, based in part on the concentration found to be irritating.

The American National Standards Institute (ANSI) [1] acceptable concentrations of xylene in 1971 were 100 ppm as an 8-hour TWA, 200 ppm as a ceiling, and 300 ppm as an acceptable maximum for a peak above the ceiling (not more than 30 minutes' duration and encountered not more than once a day). The TWA level was intended to prevent irritation, based on human experience as reported by Nelson et al. [17] The basis for the ceiling level was also human experience [17] and a review by Gerarde. [3] No basis was given for the 300 ppm peak, but it was said that there would be no health damage, provided that such an exposure would not be encountered more than once a day, although irritation of the eyes, nose, and throat was expected.

A number of limits have been set by foreign countries. In 1968 the Joint ILO/WHO Committee on Occupational Health [36] compiled the recommendations (listed in Table X-5) from 11 countries and 6 states in the United States, with values ranging from 10-200 ppm (50-870 mg/cu m). No basis was given for any of these limits. According to Bardodej, [129] the Czechoslovakian MAC was established on the basis of experience showing that the mean MAC of 200 mg/cu m (45 ppm) posed no hazard of damage after long-term exposure, and that the peak MAC of 1,000 mg/cu m (230 ppm) presented

no risk of acute poisoning. Bardodej cited his own unpublished work showing no health damage after exposure at 200 mg/cu m, although there were "single complaints by employees about headache and loss of appetit (sic), in exceptional cases drowsiness...." He also reported that unacclimatized persons complained of slight irritation of the eyes and "airways."

The present federal standard for occupational exposure to xylene is 100 ppm as a TWA. [29 CFR 1910.93, published in the Federal Register, vol 39, June 27, 1974] This was based on the ACGIH TLV in 1968.

Basis for Recommended Environmental Standard

Xylene can have a narcotic effect, apparently at relatively high levels, but actual air concentrations have not been reported. Johnstone and Miller [77] speculated that workers would not voluntarily remain in such an atmosphere long enough for the symptoms to develop because of the irritating nature of xylene. While this may make narcosis less probable, Morley et al [24] reported 3 cases (1 of which was fatal) and Sikora and Gala [29] reported 1 case in which workers, who were not trapped and could have escaped, were overcome by xylene vapor. No atmospheric concentrations were reported, but Morley et al [24] estimated the air level had reached 10,000 ppm. Glass [23] reported that a worker intermittently exposed for 2 weeks at concentrations of 270-350 ppm, and probably at higher concentrations on occasion, developed giddiness and vomiting, followed by anorexia for 1 week.

Liver damage [24] and kidney damage [24,26] have been reported after inhalation of xylene and liver damage [25] after the accidental ingestion of a small amount of a xylene-toluene thinner. In all these cases,

exposure was sufficient to cause unconsciousness [24] or illness, [25,26] but all those involved recovered fully. No published evidence was found of irreversible liver or kidney damage. Liver necrosis and diffuse nephritis have been reported after xylene was injected intraperitoneally in rats, and moderate cloudy swelling of the kidneys followed exposure by inhalation. [38] DiVincenzo and Krasavage [71] recently reported lipid deposition in the liver and increased serum OCT activity after xylene was injected intraperitoneally in guinea pigs.

There have been reports of reversible corneal vacuolization resulting from exposure to xylene [28] or xylene plus other volatile solvents [27] in the furniture polishing industry. Two investigators reported similar transient vacuolization when cats were exposed to xylene vapor [27] and when xylene was instilled in the eyes of rabbits. [43] More recently, efforts to produce this effect failed [CP Carpenter, DL Geary, written communication, April 1974] when rabbits were exposed to xylene vapor, had xylene instilled in an eye, or were given xylene by intratracheal tube.

In the past, xylene was thought to be myelotoxic based on reports that occupational exposures had led to leukopenia, [10] relative lymphocytosis, [10,12] and aplastic anemia. [12-15] In animal studies, changes that have been reported include transitory leukopenia, [38] leukocytosis, [65] and hyperplasia of the bone marrow. [38,64,66] Aplasia of the bone marrow has not been reported after administration of xylene, but has followed benzene exposure. [38,68,69]

In all of the occupational exposures to xylene, concomitant benzene exposure was either known or suspected at some time in the individual's career. Since benzene is known to cause the kinds of blood dyscrasias

reported, [116] the myelotoxicity can be attributed to benzene rather than xylene exposure. This conclusion is supported by 2 recent animal studies [19,70] in which exposure to pure xylene did not produce significant hematologic changes in rats, dogs, guinea pigs, or monkeys, although benzene has induced aplasia in other animal studies. [38,68,69] On this basis, it is concluded that xylene is not myelotoxic when uncontaminated with substances such as benzene. This conclusion that xylene is not myelotoxic was also expressed in review articles by Browning, [2,73] Gerarde, [3,72,74,75] Johnstone and Miller, [77] Lederer, [78] and by Lehmann and Flury. [76]

Thus, the only well-documented effects which a xylene standard should protect against are the irritating and narcotizing properties of xylene. There are no data available from actual occupational exposures, but these effects have been investigated experimentally. One study [40] indicated that narcotic effects were observed in mice at concentrations over 2,000 ppm, while another [42] reported that some mice died after a 24-hour exposure to m-xylene at a concentration of 2,010 ppm. For humans, only one report was found which associated possible narcotic effects with a known xylene concentration. One of 7 volunteers exposed at 1.0 mg/liter (230 ppm) and 1 of 6 exposed at 2.0 mg/liter (460 ppm) [19] experienced slight lightheadness without loss of equilibrium or coordination at the end of the 15-minute exposure period.

Estimates of the odor threshold for xylene range from 0.6 mg/cu m (0.14 ppm) [21] to 20 ppm. [18] Although there was a wide difference in the odor thresholds, these authors [18,21] both reported a lower threshold for xylene than for toluene. Similarly, Nelson et al [17] found that

xylene was more irritating than toluene to the eyes and mucous membranes during a 3- to 5-minute exposure. Based on this brief exposure, these subjects estimated that 100 ppm would be satisfactory for an 8-hour exposure. Based on 15-minute exposures, Carpenter et al [19] concluded that 1.0 mg/liter (230 ppm) should not be objectionable to most people.

While there are no adequate data available with which to establish a xylene limit, neither are there data which indicate any need to alter the existing federal limit of 100 ppm. However, this TWA limit does not restrict excursions so long as the 8-hour TWA limit is not exceeded. Such a restriction is needed for xylene not only because of its irritant properties, but also because as a central nervous system depressant, xylene might at briefly high concentrations affect attention, judgment, or perception sufficiently that if an emergency were to occur the worker might not respond appropriately. The study by Carpenter et al [19] suggests the possibility of minimal narcotic effects at a xylene concentration of 230 ppm. Therefore, in addition to the 100 ppm TWA, NIOSH recommends a 10-minute ceiling of 200 ppm for xylene.

It is recognized that many workers handle small amounts of xylene or work in situations where, regardless of the amount used, there is only negligible contact with the substance. Under these conditions, it should not be necessary to comply with many of the provisions of this recommended standard, which has been prepared primarily to protect worker health under more hazardous circumstances. Concern for worker health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. For these reasons, "exposure to xylene" has been defined as exposure above half the environmental limit, thereby

delineating those work situations which do not require the expenditure of health resources, of environmental and medical monitoring, and associated recordkeeping. Half the environmental limit has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard may exist. However, because of nonrespiratory hazards such as those resulting from skin irritation or eye contact, it is recommended that appropriate work practices and protective measures be required regardless of the air concentration.

The absence of data either in support of or in opposition to the existing limit of 100 ppm (or the prior ACGIH TLV of 200 ppm) apparently is due to the fact that no epidemiological studies have been attempted. While exposures to a pure solvent are rare, some effort is needed to describe what effects, if any, result from occupational exposures under current conditions. Some investigators have suggested effects on the liver, [12,24,25] the kidney, [24,26] the cardiovascular system, [12,29] and the gastrointestinal tract [23] after inhalation of xylene vapor. Effects on these organs and systems should be investigated to confirm or deny any involvement of xylene. Additionally, studies should be conducted to investigate the possibility of interaction between xylene and alcohol. Earlier reports [27,28] of corneal vacuolization were not confirmed by a recent animal study [19] but workers exposed to xylene should be examined to verify that no hazard exists for them. Although the recommended standard should prevent any narcotizing effects, including impaired judgment or reaction time, studies are needed for confirmation.

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VII. APPENDIX I

SAMPLING FOR XYLENE

The sampling and analytical methods presented in Appendices I and II are based on those described by White et al, [95] Kupel and White, [130] and in Method No. 127 of the Physical and Chemical Analysis Branch of NIOSH. [100]

Atmospheric Sampling

Breathing zone samples representative of the individual worker's exposure shall be collected. A description of sampling location and conditions, equipment used, time and rate of sampling, and any other pertinent information shall be recorded at the time of sample collection. Enough samples shall be collected to permit calculation of a time-weighted average (TWA) exposure for every operation or location in which there is exposure to xylene.

(a) Equipment

The sampling train consists of a charcoal tube and vacuum pump.

(1) Charcoal tubes: Glass tubes, with both ends flame-sealed, 7-cm long with a 6-mm OD and a 4-mm ID, containing 2 sections of 20/40 mesh activated charcoal separated by a 2-mm portion of polyurethane foam. The primary section contains 100 mg of charcoal, the backup section, 50 mg. A 3-mm portion of polyurethane foam is placed between the outlet end of the tube and backup section. A plug of glass wool is placed in front of the primary section. The pressure drop across the tube must be

less than 1 inch of mercury at a flowrate of 1 liter/min. Tubes with the above specifications are commercially available.

(2) Pump: A battery-operated pump, complete with clip for attachment to the worker's belt, capable of operation at 1 liter/min or less.

(b) Calibration

Since the accuracy of an analysis can be no greater than the accuracy of the volume of air which is measured, the accurate calibration of a sampling pump is essential to the correct interpretation of the volume indicated. The frequency of calibration is dependent on the use, care, and handling to which the pump is subjected. Pumps should also be recalibrated if they have been misused or if they have just been repaired or received from a manufacturer. If the pump receives hard usage, more frequent calibration may be necessary. Regardless of use, maintenance and calibration should be performed on a regular schedule and records of these kept.

Ordinarily, pumps should be calibrated in the laboratory both before they are used in the field and after they have been used to collect a large number of field samples. The accuracy of calibration is dependent on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, primary standards such as a spirometer or soapbubble meter are recommended, although other standard calibrating instruments such as a wet test meter or dry gas meter can be used. The actual setups will be similar for all instruments.

Instructions for calibration with the soapbubble meter follow. If another calibration device is selected, equivalent procedures should be

used. The calibration setup for personal sampling pumps with a charcoal tube is shown in Figure X-1. Since the flowrate given by a pump is dependent on the pressure drop of the sampling device, in this case a charcoal tube, the pump must be calibrated while operating with a representative charcoal tube in line.

(1) The voltage of the pump battery is checked with a voltmeter to assure adequate voltage for calibration. The battery is charged if necessary.

(2) The tips of a charcoal tube are broken to produce openings of at least 2 mm in diameter.

(3) The sampling train is assembled as shown in Figure X-1.

(4) The pump is turned on and the inside of the soapbubble meter is moistened by immersing the buret in the soap solution and drawing bubbles up the inside until they are able to travel the entire buret length without bursting.

(5) The pump rotameter is adjusted to provide the desired flowrate.

(6) The water manometer is checked to insure that the pressure drop across the sampling train does not exceed 13 inches of water at 1 liter/min or 2.5 inches of water at 200 ml/min.

(7) A soapbubble is started up the buret and the time it takes the bubble to move from one calibration mark to another is measured with a stopwatch.

(8) The procedure in (7) above is repeated at least twice, the results averaged, and the flowrate calculated by dividing the volume between the preselected marks by the time required for the soapbubble to

traverse the distance. If, for the pump being calibrated, the volume of air sampled is calculated as the product of the number of strokes times a stroke factor (given in units of volume/stroke), the stroke factor is the quotient of the volume between the 2 preselected marks divided by the number of strokes.

(9) Data for the calibration include the volume measured, elapsed time or number of strokes, pressure drop, air temperature, atmospheric pressure, serial number of the pump, date, and name of the person performing the calibration.

(c) Sampling Procedure

(1) Both ends of the charcoal tube are broken to provide openings of at least 2 mm, which is half the ID of the tube. A smaller opening causes a limiting orifice effect which reduces the flow through the tube. The smaller section of charcoal in the tube is used as a backup section and therefore is placed nearest the sampling pump. Tubing is used to connect the back of the tube to the pump, but tubing must never be put in front of the charcoal tube. The tube is supported in a vertical position in the worker's breathing zone.

(2) A maximum of 15 liters of air is sampled at a flowrate of 50-1,000 ml/min. For the determination of ceiling concentrations the sampling time is 10 minutes. For the determination of 8-hour time-weighted average concentrations 2 4-hour or 4 2-hour samples are suggested.

(3) The temperature and pressure of the atmosphere being sampled is measured and recorded.

(4) One charcoal tube is treated in the same manner as the sample tubes (break, seal, ship) with the exception that no air is drawn

through it. This tube serves as a blank.

(5) Immediately after sampling, charcoal tubes are capped with plastic caps. Under no circumstances should rubber caps be used. To minimize breakage during transport, capped tubes should be tightly packed in a shipping container. Bulk samples and charcoal tubes should be shipped separately.

VIII. APPENDIX II

ANALYTICAL METHOD FOR XYLENE

Principle of the Method

Xylene vapor trapped on charcoal from a known volume of air is desorbed with carbon disulfide. An aliquot of the desorbed sample is injected into a gas chromatograph. The area of the resulting peak is determined and compared with areas obtained from injection of standards.

Range and Sensitivity

The lower limit of detection of the analytical procedure was found to be less than 12 μg/sample.

Interferences

When the amount of water in the air is so great that condensation actually occurs in the tube, organic vapors will not be trapped. Preliminary experiments indicate that high humidity severely decreases the amount of organic vapor which can be collected before breakthrough of the primary adsorbing section occurs. The capacity of the charcoal tube for xylene may also be reduced by the presence of another organic vapor in high concentration.

Any compound which has about the same retention time as one of the xylene isomers at the gas chromatographic conditions described in this method will interfere with the analysis. This type of interference can be

overcome by changing the operating conditions of the instrument, usually the column and/or the column temperature.

Precision and Accuracy

In a collaborative test, [101] the total relative error in the range of 60-200 ppm (260-870 mg/cu m) was 9.5%. At approximately 5 ppm (20 mg/cu m) this error was 13%.

Advantages and Disadvantages of the Method

The sampling device is small, portable, and involves no liquids. Interferences are minimal and most can be eliminated by altering the chromatographic conditions. The analysis is accomplished using a rapid instrumental method, which can also be used for the simultaneous analysis of 2 or more solvents present in the same sample by changing gas chromatographic conditions from isothermal to a temperature-programmed mode of operation.

One disadvantage of the method is that the amount of sample which can be taken is limited by the number of milligrams that the tube will hold before overloading. When the sample value obtained for the backup section of the charcoal trap exceeds 20% of that found on the front section, the possibility of sample loss exists.

The precision of the method is limited by the reproducibility of the pressure drop across the tubes. This drop will affect the flow rate and cause the volume to be imprecise, because the pump is usually calibrated for one tube only.

Apparatus

(a) Gas chromatograph equipped with a flame ionization detector.

(b) Column (20 ft x 1/8 in) with 10% FFAP stationary phase on 80/100 mesh acid washed DMCS Chromosorb W solid support. Other columns which achieve the desired separation may be used.

(c) A mechanical or electronic integrator or a recorder and some method for determining peak area.

(d) Small glass-stoppered test tubes or equivalent.

(e) Syringes: 10-μl, and convenient sizes for preparation of standards.

Reagents

(a) Carbon disulfide, chromatographic quality.

(b) Xylene, preferably having an isomer distribution close to that of the sample.

(c) Bureau of Mines Grade A helium.

(d) Prepurified hydrogen.

(e) Filtered compressed air.

Analysis of Samples

All glassware used for the laboratory analysis should be washed in detergent followed by tap and distilled water rinses.

(a) Preparation: Each charcoal tube, including the blank from field samples, is scored with a file and broken open in front of the first section of charcoal. The glass wool is removed and discarded. The

charcoal in the first (larger) section is transferred to a small stoppered test tube. The foam separating section is removed and discarded, and the second section of charcoal is transferred to another test tube. The 2 charcoal sections are then analyzed separately.

(b) Desorption: Prior to analysis, 0.5 ml of carbon disulfide is pipetted into each test tube to desorb the xylene from the charcoal. Desorption is complete in 30 minutes if the sample is stirred occasionally.

EXTREME CAUTION MUST BE EXERCISED AT ALL TIMES WHEN USING CARBON DISULFIDE BECAUSE OF ITS HIGH TOXICITY AND FIRE AND EXPLOSION HAZARDS. IT CAN BE IGNITED BY HOT STEAM PIPES. ALL WORK WITH CARBON DISULFIDE MUST BE PERFORMED UNDER AN EXHAUST HOOD.

(c) Typical gas chromatographic operating conditions:

(1) 40 cc/min (70 psig) helium carrier gas flow.

(2) 65 cc/min (24 psig) hydrogen gas flow to detector.

(3) 500 cc/min (50 psig) airflow to detector.

(4) 200 C injector temperature.

(5) 200 C manifold temperature (detector).

(6) 110 C isothermal oven or column temperature.

(d) Injection: The first step in the analysis is the injection of the sample into the gas chromatograph. The solvent flush injection technique is employed. This eliminates difficulties arising from blowback or distillation within the syringe needle, thus increasing the accuracy and reproducibility of the injected sample volume. The 10.0-μl syringe is first flushed with solvent several times to wet the barrel and plunger, then 3.0 μl of solvent are drawn into the syringe. Next, the needle is removed from the solvent and the plunger is pulled back about 0.2 μl to

separate the solvent flush from the sample with an air pocket to be used as a marker. The needle is then immersed in the sample and a 5.0-μl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection in the gas chromatograph, the plunger is pulled back a short distance to minimize sample evaporation from the needle tip. Duplicate injections should be made of each sample and of the standard. No more than a 3% difference should result in the peak areas that are recorded.

(e) Measurement of area: The areas of the sample peaks are measured by an electronic integrator or some other suitable form of area measurement and preliminary sample results are read from a standard curve prepared as outlined below. The integration of the signals from all three xylene isomers is recommended.

Determination of Desorption Efficiency

The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus it is necessary to determine at least once the percentage of xylene that is removed in the desorption process. This procedure should be repeated for each new batch of charcoal used. The Physical and Chemical Analysis Branch of NIOSH has found desorption efficiencies for xylene varying from 92-99% between batches.

Activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) is measured into a 5-cm, 4-mm ID glass tube, flame-sealed at one end. This charcoal must be from the same batch as that

used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with Parafilm or equivalent. A known amount of xylene is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more Parafilm or equivalent. A known amount injected is usually equivalent to that present in a 10-liter sample at a concentration equal to the federal limit of 100 ppm, or about 4.3 mg.

At least 5 tubes are prepared in this manner and allowed to stand overnight or longer to assure complete adsorption of the xylene onto the charcoal. These 5 tubes are referred to as the samples. A parallel blank tube should be treated in the same manner except that no xylene is added to it. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube described for unknown air samples.

Two or 3 standards are prepared by injecting the same volume of xylene into 0.5 ml of carbon disulfide with the same syringe used in the preparation of the sample. These are analyzed with the samples.

The desorption efficiency equals the difference between the average peak area of the samples and the peak area of the blank divided by the average peak area of the standards, or:

$$\text{desorption efficiency} = \frac{\text{area sample - area blank}}{\text{area standard}}$$

Calibration and Standards

It is convenient to express the concentration of standards in terms of mg/0.5 ml carbon disulfide, because samples are desorbed in this amount of carbon disulfide. The density of the xylene is used to convert

milligrams into microliters for easy measurement with a microliter syringe. A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/0.5 ml versus peak area.

Calculations

The weight in mg, corresponding to the total peak area, is read from the standard curve. No volume corrections are needed, because the standard curve is based on mg/0.5 ml carbon disulfide and the volume of sample injected is identical to the volume of the standards injected.

Corrections for the blank from the field sampling are made for each sample by subtracting the amounts of xylene found on the front and back sections of the blank from the amounts found in the respective sections of the sample:

Corrected amount = amount on sample - amount on blank

The corrected amounts present in the front and backup sections of the same sample tube are added to determine the total amount of xylene in the sample. This total amount is divided by the desorption efficiency to obtain the adjusted total amount of xylene in the sample.

The volume of air sampled is converted to standard conditions of 25 C and 760 mm Hg:

$$\text{Adjusted total amount} = \frac{\text{total amount}}{\text{desorption efficiency}}$$

The concentration of xylene in the air sampled, expressed in mg/cu m (which is numerically equal to μg/liter of air) is given by the quotient of the adjusted amount in μg divided by the volume of air sampled in liters:

$$\text{concentration } (\mu g/\text{liter}) = \frac{\text{adjusted amount } (\mu g)}{\text{volume (liters)}}$$

Another method of expressing concentration is ppm:

$$\text{concentration (ppm)} = \text{concentration } (\mu g) \times \frac{24.45}{106} \times \frac{760}{P} \times \frac{(T + 273)}{298}$$

where:

24.45 = molar volume (liter/mole) at 25 C and 760 Torr

106 = molecular weight of xylene (g/mole)

760 = standard pressure

P = pressure (Torr) of air sampled

T = temperature (degrees C) of air sampled

298 = standard temperature (degrees K)

or

$$\text{concentration (ppm)} = \text{concentration } (\mu g) \times \frac{0.588\ (T + 273)}{P}$$

IX. APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material containing xylene shall be provided in the appropriate section of the Material Safety Data Sheet or other approved form. If a specific item of information is inapplicable (eg, flash point), the initials "na" (not applicable) should be inserted.

(a) Section I. Source and Nomenclature.

(1) The name, address, and telephone number of the manufacturer or supplier of the product.

(2) The trade name and synonyms for a mixture of chemicals, a basic structural material, or for a process material; and the trade name and synonyms, chemical name and synonyms, chemical family, and formula for a single chemical.

(b) Section II. Hazardous Ingredients.

(1) Chemical or widely recognized common name of all hazardous ingredients.

(2) The approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, eg, 10-20% by volume; 10% maximum by weight.

(3) Basis for toxicity for each hazardous material such as an established standard, in appropriate units.

(c) Section III. Physical Data.

Physical properties of the total product including boiling point and melting point in degrees Fahrenheit; vapor pressure, in millimeters of mercury, vapor density of gas or vapor (air = 1), solubility in water, in parts per hundred parts of water by weight; specific gravity (water = 1); percent volatile (indicate if by weight or volume) at 70 Fahrenheit; evaporation rate for liquids (indicate whether butyl acetate or ether = 1); and appearance and odor.

(d) Section IV. Fire and Explosion Hazard Data.

Fire and explosion hazard data about a single chemical or a mixture of chemicals, including flash point, in degrees Fahrenheit; flammable limits, in percent by volume in air; suitable extinguishing media or agents; special firefighting procedures; and unusual fire and explosion hazard information.

(e) Section V. Health Hazard Data.

Toxic level for total compound or mixture, effects of exposure, and emergency and first aid procedures.

(f) Section VI. Reactivity Data.

Chemical stability, incompatibility, hazardous decomposition products, and hazardous polymerization.

(g) Section VII. Spill or Leak Procedures.

Detailed procedures to be followed with emphasis on precautions to be taken in cleaning up and safe disposal of materials leaked or spilled. This includes proper labeling and disposal of containers containing residues, contaminated absorbents, etc.

(h) Section VIII. Special Protection Information.

Requirements for personal protective equipment, such as respirators, eye protection and protective clothing, and ventilation such as local exhaust (at site of product use or application), general, or other special types.

(i) Section IX. Special Precautions.

Any other general precautionary information.

U.S. DEPARTMENT OF LABOR
Occupational Safety and Health Administration

Form Approved
OMB No. 44-R1387

MATERIAL SAFETY DATA SHEET

Required under USDL Safety and Health Regulations for Ship Repairing, Shipbuilding, and Shipbreaking (29 CFR 1915, 1916, 1917)

SECTION I

MANUFACTURER'S NAME	EMERGENCY TELEPHONE NO.
ADDRESS *(Number, Street, City, State, and ZIP Code)*	
CHEMICAL NAME AND SYNONYMS	TRADE NAME AND SYNONYMS
CHEMICAL FAMILY	FORMULA

SECTION II - HAZARDOUS INGREDIENTS

PAINTS, PRESERVATIVES, & SOLVENTS	%	TLV (Units)	ALLOYS AND METALLIC COATINGS	%	TLV (Units)
PIGMENTS			BASE METAL		
CATALYST			ALLOYS		
VEHICLE			METALLIC COATINGS		
SOLVENTS			FILLER METAL PLUS COATING OR CORE FLUX		
ADDITIVES			OTHERS		
OTHERS					

HAZARDOUS MIXTURES OF OTHER LIQUIDS, SOLIDS, OR GASES	%	TLV (Units)

SECTION III - PHYSICAL DATA

BOILING POINT (°F.)		SPECIFIC GRAVITY (H_2O=1)	
VAPOR PRESSURE (mm Hg.)		PERCENT, VOLATILE BY VOLUME (%)	
VAPOR DENSITY (AIR=1)		EVAPORATION RATE (_____ =1)	
SOLUBILITY IN WATER			
APPEARANCE AND ODOR			

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (Method used)	FLAMMABLE LIMITS	Lel	Uel

EXTINGUISHING MEDIA
SPECIAL FIRE FIGHTING PROCEDURES
UNUSUAL FIRE AND EXPLOSION HAZARDS

(Continued on reverse side)

SECTION V - HEALTH HAZARD DATA

THRESHOLD LIMIT VALUE

EFFECTS OF OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

SECTION VI - REACTIVITY DATA

STABILITY	UNSTABLE		CONDITIONS TO AVOID
	STABLE		

INCOMPATIBILITY *(Materials to avoid)*

HAZARDOUS DECOMPOSITION PRODUCTS

HAZARDOUS POLYMERIZATION	MAY OCCUR		CONDITIONS TO AVOID
	WILL NOT OCCUR		

SECTION VII - SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED

WASTE DISPOSAL METHOD

SECTION VIII - SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION *(Specify type)*

VENTILATION	LOCAL EXHAUST	SPECIAL
	MECHANICAL *(General)*	OTHER

PROTECTIVE GLOVES	EYE PROTECTION

OTHER PROTECTIVE EQUIPMENT

SECTION IX - SPECIAL PRECAUTIONS

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORING

OTHER PRECAUTIONS

GPO 934-110

X. TABLES AND FIGURE

TABLE X-1

PHYSICAL PROPERTIES OF XYLENE ISOMERS

	o-xylene	m-xylene	p-xylene
Specific gravity (25/4 C)	0.8758	0.8598	0.8567
Vapor density (air = 1)	3.7	3.7	3.7
Freezing point	-25.2 C	-47.9 C	+13.3 C
Boiling point	144.4 C	139.1 C	138.4 C
Density of saturated vapor-air mixture at 760 mm and 25 C (air = 1)	1.02	1.03	1.03
Flammable limits (% in air)	1.1-6.4	1.1-6.4	1.1-6.6
Vapor pressure (mm Hg) at 25 C	5.2	8.3	8.6
Flash point (closed cup)	17.2 C	25.0 C	25.0 C
Conversion factors (760 mm and 25 C)	1 ppm = 4.35 mg/cu m 1 mg/cu m = 0.230 ppm		

from ANSI Z37.10-1971 [1]

TABLE X--2

HUMAN SENSORY THRESHOLDS FOR MIXED XYLENES

Measured Concentration (ppm)	106	233	454
Number:			
Volunteers	6	7	6
Detecting Odor	6	7	6
Olfactory Fatigue	3	3	3
Throat Irritation	1	0	1
Eye Irritation	0	1	4
With Tears	0	1	1
Reporting Dizziness	0	1	1
Tasting "Something"	0	1	0
With Effects 10 min after Exposure	0	0	0

from Carpenter et al [19]

TABLE X-3

URINARY EXCRETION OF METHYLHIPPURIC ACID AFTER XYLENE EXPOSURE

Sampling (hours)		0-3			4-8			0-8		
		m-xylene		p-xylene	m-xylene		p-xylene	m-xylene		p-xylene
ppm		100	200	100	100	200	100	100	200	100
Uncorrected	Mean	1.75	3.59	2.11	3.14	5.79	1.42	1.86	4.56	1.45
(mg/ml)	SD	0.85	0.65	1.27	1.50	0.91	0.10	0.48	0.49	0.10
Corrected	Mean	1.78	3.19	2.26	2.63	5.58	3.09	2.39	5.32	2.50
(mg/ml)	SD	0.61	0.46	0.96	0.75	1.33	0.82	0.33	0.24	0.69
Rate	Mean	1.69	3.89	1.56	2.16	4.49	2.11	1.78	4.10	1.75
(mg/min)	SD	0.29	0.89	0.23	0.19	1.15	0.77	0.34	0.84	0.21

from Ogata et al [112]

TABLE X-4

SCREENING LEVELS OF METHYLHIPPURIC ACID IN URINE OF WORKERS EXPOSED TO m-XYLENE OR p-XYLENE

	Exposure period (hours)		
	7 (mg/min)	0-3 (mg/ml)	4-8
m-xylene	1.10	0.56	1.13
p-xylene	1.33	0.34	1.45

from Ogata et al [112]

TABLE X-5

XYLENE EXPOSURE LIMITS

Country	mg/cu m	ppm
Bulgaria	100	23*
Czechoslovakia	200	46
(Single Exposure)	1,000	230
Finland	870	200
Germany (Federal Republic)	870	200
Hungary	50	12*
Japan	670	150
Poland	100	23*
Rumania	200	46*
United States	870	200
Florida	870*	200
Hawaii	870*	200
Massachusetts	435*	100
Mississippi	870*	200
Pennsylvania	870*	200
(30-minutes)	1,300*	300
South Carolina	870*	200
USSR	50	12*
Yugoslavia	400	100

*Equivalent values calculated by NIOSH from reference 36

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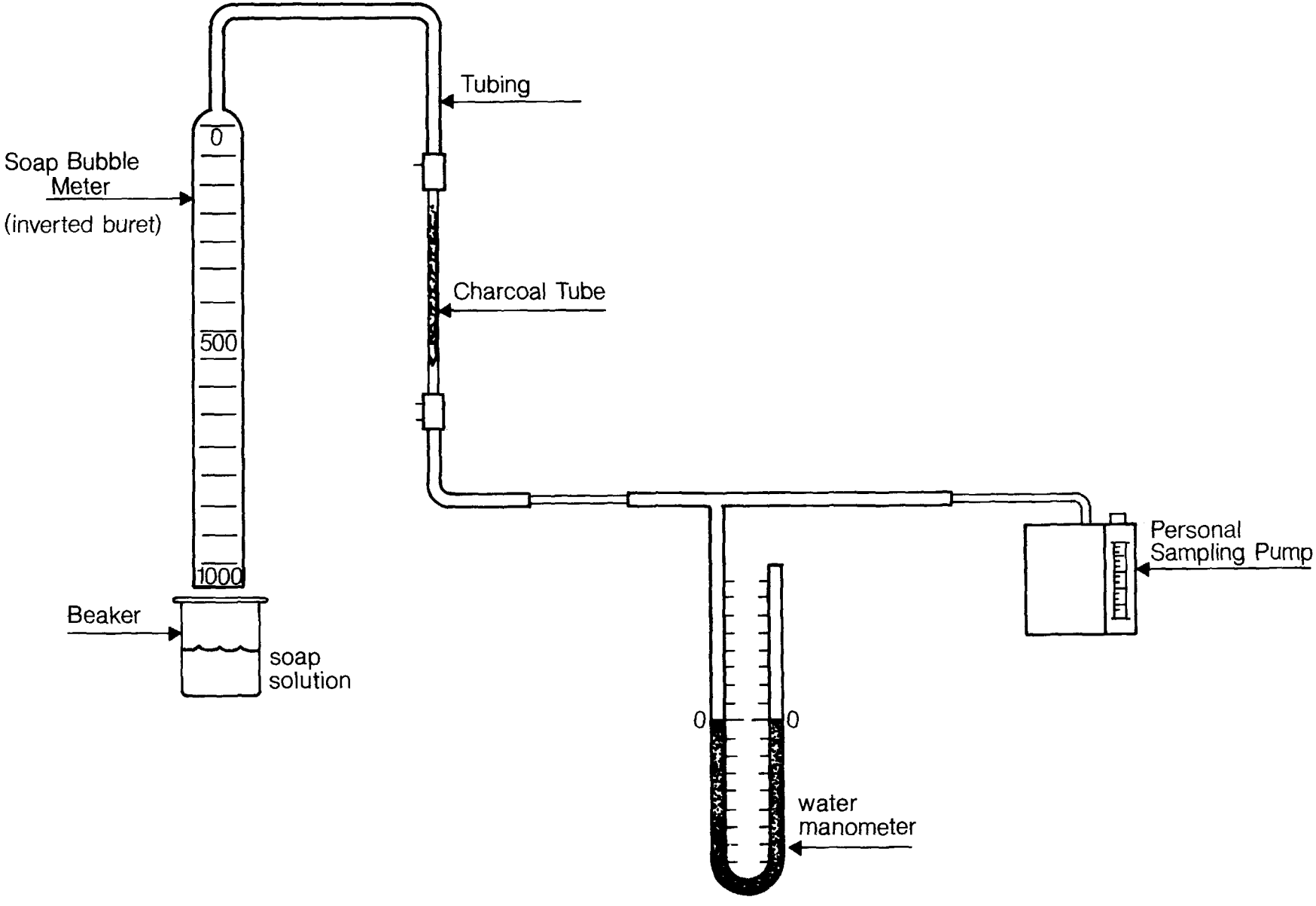
FIGURE X-1

CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH CHARCOAL TUBE



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HEW Publication No. (NIOSH) 75–168